Importance of Different Pathways of Cellular Cholesterol Efflux

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Abstract—The removal of excess free cholesterol from cells by HDL or its apolipoproteins is important for maintaining cellular cholesterol homeostasis. This process is most likely compromised in the atherosclerotic lesion because the development of atherosclerosis is associated with low HDL cholesterol. Multiple mechanisms for efflux of cell cholesterol exist. Efflux of free cholesterol via aqueous diffusion occurs with all cell types but is inefficient. Efflux of cholesterol is accelerated when scavenger receptor class-B type I (SR-BI) is present in the cell plasma membrane. Both diffusion-mediated and SR-BI–mediated efflux occur to phospholipid-containing acceptors (ie, HDL and lipidated apolipoproteins); in both cases, the flux of cholesterol is bidirectional, with the direction of net flux depending on the cholesterol gradient. The ATP-binding cassette transporter AI (ABCA1) mediates efflux of both cellular cholesterol and phospholipid. In contrast to SR-BI–mediated flux, efflux via ABCA1 is unidirectional, occurring to lipid-poor apolipoproteins. The relative importance of the SR-BI and ABCA1 efflux pathways in preventing the development of atherosclerotic plaque is not known but will depend on the expression levels of the two proteins and on the type of cholesterol acceptors available. (Arterioscler Thromb Vasc Biol. 2003;23:lll–lll.)

Key Words: cholesterol efflux ■ scavenger receptor class-BI ■ ATP-binding cassette transporter AI ■ reverse cholesterol transport

HDL levels are inversely correlated with the incidence of coronary artery disease. A long-standing hypothesis to explain this protective effect of HDL against atherosclerosis is the process of reverse cholesterol transport (RCT). In RCT, HDL or its apolipoproteins mediate the removal of excess free cholesterol (FC) from peripheral cells and, after a series of reactions in plasma, the cholesterol is delivered via either LDL or HDL to the liver for excretion into the bile. The flux of FC between cells and extracellular acceptors is important at two points in the RCT pathway: (1) the removal of FC from peripheral cells and (2) the delivery of HDL FC to the liver. There are 3 known mechanisms of FC flux: (1) aqueous diffusion, (2) SR-BI-mediated FC flux, and (3) ABCA1-mediated efflux (Figure 1). The purpose of this review is to discuss each mechanism and the relative importance of each mechanism to RCT.

Aqueous Diffusion
Cholesterol molecules are sufficiently water-soluble to be able to transfer from either model6 or cell membranes7 to an acceptor by the so-called aqueous diffusion mechanism. This process involves desorption of cholesterol molecules from the donor lipid-water interface and diffusion of these molecules through the intervening aqueous phase until they collide with and are absorbed by an acceptor. At a constant donor particle concentration, there is a hyperbolic dependence of cholesterol transfer rate on the concentration of acceptor particles; the kinetics can be described in terms of the rate constants for movement of cholesterol molecules on and off the donor and acceptor surfaces. At lower acceptor concentrations, the transfer rate is dependent on the frequency of diffusion-mediated collisions between cholesterol molecules and acceptor particles. The unstirred water layer surrounding cells creates a significant diffusion barrier. At high acceptor particle concentrations, the transfer rate is dependent on the frequency of diffusion-mediated collisions between cholesterol molecules and acceptor particles. The unstirred water layer surrounding cells creates a significant diffusion barrier. At high acceptor particle concentrations, the desorption of cholesterol molecules from the surface of the donor particle becomes the rate-limiting step; there is a high activation energy associated with this step, and cholesterol transfer rates are strongly temperature-dependent. The activation energy and the rate of transfer are affected by the interactions of the desorbing cholesterol molecule with its phospholipid neighbors in the lipid-water interface. Factors that reduce the lipid molecular packing density tend to enhance the rate of cholesterol transfer. Examples of such factors include high-surface cur-
vature, phospholipid acyl chain unsaturation, and low sphingomyelin to phosphatidylcholine (PC) ratio.8,10

The aqueous diffusion mechanism involves a simple diffusion process, and, as such, cholesterol transfer is passive and driven by the cholesterol concentration gradient. When a cholesterol-containing lipoprotein particle such as HDL is incubated with cells, a bidirectional flux of cholesterol occurs between the HDL particles and the cell plasma membrane.11 Exchange of cholesterol mass occurs when efflux and influx are equal. Net transfer of cholesterol mass in either direction can occur by mass action effects when either the cell membrane or HDL are relatively enriched in cholesterol. Because cholesterol in lipoproteins and membranes is solubilized in phospholipid, net transfer of cholesterol between cells and HDL is promoted by processes that either elevate the free cholesterol/phospholipid ratio of the prospective donor or reduce this ratio in the prospective acceptor.11

The rate of cellular cholesterol efflux by the aqueous diffusion mechanism is highly dependent on the structure of the acceptor particle.12 The size of the acceptor particle is important because it affects the diffusion-mediated collisions with cholesterol molecules present in the aqueous phase. Large particles are inefficient acceptors. Thus, the same concentration of phospholipid present as a discoidal complex with apo AI (>200 phospholipid molecules/particle) promotes approximately 4-times faster efflux from human skin fibroblasts than when it is present as a small unilamellar vesicle (>2000 phospholipid molecules/particle).9 Small molecules such as cyclodextrins promote rapid cholesterol efflux because they can diffuse very close to the plasma membrane.13 Cyclodextrins have a low capacity to accept cellular cholesterol, but they act as efficient shuttles when present together with a high capacity acceptor particle, such as a phospholipid liposome.12 Serum albumin may play such a shuttle role in mediating transfer of cholesterol from cells to lipoproteins.14

The transfer of cholesterol from phospholipid bilayers by the aqueous diffusion mechanism occurs in the time scale of hours. For example, the halftime for transfer of cholesterol from egg PC/cholesterol small unilamellar vesicles at 37°C is >1 hour.8 In comparison, the half-times for efflux of cholesterol from different types of cells to HDL are on the order of 10 hours.12 The structure of the plasma membrane influences the halftime, and, as discussed below, the aqueous diffusion process may be facilitated by membrane proteins.

**SR-BI–Mediated FC Flux**

Early studies showed that different kinds of cells exhibit large differences in the rates of cholesterol efflux to phospholipid-containing acceptors.15 Recent studies have shown that these differences are attributable to differences in the expression levels of SR-BI.16,17 Additional evidence for SR-BI mediating FC efflux is that efflux is accelerated from COS-7 cells transiently transfected with SR-BI compared with efflux from control COS-7 cells.18 Besides stimulating the efflux of FC, expression of SR-BI also facilitates the influx of FC. Thus, movement of FC via SR-BI is bidirectional, and, like the aqueous diffusion mechanism, the net movement of FC via SR-BI depends on the direction of the cholesterol gradient.19–21 Besides mediating the bidirectional flux of FC, SR-BI mediates the selective uptake of other lipoprotein lipids, including cholesteryl ester, phospholipid, and triglyceride.22 This movement is unidirectional, and by mediating the net flux of HDL cholesteryl ester and triglyceride, SR-BI promotes depletion of HDL core lipids.23 SR-BI is a member of the CD36 family of proteins and shares ~30% sequence homology with the other members of this family.23,24 It is predicted to have a large extracellular domain (408 aa) that is heavily N-glycosylated and contains 6 cysteine residues.23,25 The extracellular domain is anchored at the N- and C-termini by transmembrane domains that have short extensions into the cytoplasm.25 Studies using chimeric
receptors composed of various domains from either CD36 or SR-BI have shown that the extracellular domain of SR-BI is crucial for mediating the bidirectional flux of FC.27 This domain has been proposed to form a nonpolar channel that facilitates the movement of lipid molecules between bound lipoproteins and the plasma membrane.22,28

SR-BI is a multi-ligand receptor that interacts with a broad range of acceptors, including HDL, LDL, oxidized LDL, acetylated LDL, and small unilamellar vesicles.29 There is an absolute requirement for phospholipid in the acceptor, because no efflux to lipid-free apolipoproteins occurs via SR-BI, even though lipid-free apo AI has been demonstrated to bind to SR-BI.18 Indeed, SR-BI–mediated FC efflux is a function of the PC content of the acceptors. This is substantiated by studies showing that the enrichment of HDL20 or serum18 with PC increases SR-BI–mediated efflux, whereas depletion of HDL PC by treatment with phospholipase-A2 (PLA2) decreases SR-BI–mediated efflux. Additional studies, using a combination of PC enrichment and PLA2 treatment of HDL, have demonstrated that there is a strong correlation (r2=0.985) between efflux with SR-BI–expressing COS cells and HDL PC content.20 Similarly, in vivo modulation of serum phospholipids in mice affects SR-BI–mediated efflux. Thus, overexpression of either endothelial lipase or phosphatidylserine-specific phospholipase to decrease or increase serum phospholipids, respectively, decreases or increases the efflux potential of the serum via SR-BI. In addition, with both endothelial lipase and phosphatidylserine-specific phospholipase overexpression, there is a strong positive correlation between SR-BI–mediated FC efflux and the serum phospholipid to apo AI ratio (unpublished observations).

SR-BI–mediated FC flux is also sensitive to the nature of the phospholipid species. Studies have shown that in contrast to PC enrichment of HDL, only small increases in SR-BI–mediated efflux occur when HDL is enriched with sphingomyelin.20 However, large decreases in SR-BI–mediated FC influx occur when HDL is sphingomyelin enriched. Thus, both PC and sphingomyelin enrichment of HDL result in an increase in the net efflux of FC via SR-BI, but the increase is mediated by different mechanisms; with PC enrichment of HDL, the rate of efflux is increased, whereas with sphingomyelin enrichment, the rate of FC influx is decreased.20

The detailed mechanism by which SR-BI facilitates the bidirectional flux of FC remains to be elucidated. Although not proven, it is often assumed that SR-BI accelerates the diffusion mechanism of FC flux. There are data that are consistent with SR-BI facilitating an already existing mechanism in cells. Over a range of HDL doses that are below or above the Kd for HDL binding to SR-BI, there is a strong positive correlation (r2=0.994) between efflux from COS-7 cells transfected with empty vector and efflux from COS-7 cells transfected with SR-BI (Ilaria Zanotti, unpublished observation). Additional data to support the concept that SR-BI is facilitating the diffusion mechanism is that FC or sphingomyelin enrichment of HDL causes similar effects, although small, on the efflux or influx of FC with control COS-7 cells that lack SR-BI.20

The role of acceptor binding to SR-BI in facilitating efflux is somewhat controversial. Binding of the acceptor to SR-BI could possibly enhance the diffusion mechanism of FC flux by concentrating the acceptor particles at the cell surface. However, it is apparent that high-affinity binding to cell surface receptors alone is not sufficient to stimulate the flux of FC, because expression of CD36 on COS-7 cells markedly enhances high-affinity binding of HDL but only minimally increases efflux.18 Interestingly, the dose dependence of SR-BI–mediated efflux to HDL is biphasic.18,31 There is a half-maximal efflux at low concentrations of HDL (<30 μg protein/mL) that is similar to the Kd for HDL binding to SR-BI.18 This suggests that there is an efficient component of SR-BI–mediated efflux that may be strongly linked to binding of the acceptor to SR-BI. However, at higher concentrations of HDL where binding to SR-BI is saturated, SR-BI–mediated efflux to HDL still exhibits a large dependence on HDL concentration.18,31 This suggests that there is a low efficiency component of SR-BI–mediated efflux, where binding of the acceptor to SR-BI does not contribute much to the facilitation of FC flux. One way SR-BI may be facilitating the rate of desorption of FC is by reorganizing membrane lipid packing. Consistent with this concept, SR-BI expression alters the distribution of FC between kinetic pools, primarily increasing the size of a fast pool.19 Additional evidence is that SR-BI expression increases the fraction of membrane cholesterol that is susceptible to exogenous cholesterol oxidase.18,19

It is also worth noting that in some cell types, SR-BI is localized to caveolae and lipid rafts, areas of the membrane that are rich in both cholesterol and sphingomyelin.26,32

As already stated, there is an efficient component of SR-BI–mediated efflux that is probably linked to binding of the acceptor to SR-BI, and several recent studies are consistent with this concept. Studies by Gu et al31 demonstrated that an antibody that blocked HDL binding but did not decrease the cholesterol-oxidase–sensitive pool decreased FC efflux. These same studies demonstrated that a mutant SR-BI that lost most of its ability to bind HDL but retained its ability to bind LDL exhibited decreased efflux to HDL but not to LDL. However, more recently, it was shown that high-affinity binding to SR-BI alone is not enough to ensure efficient lipid transfer.33 Thus, SR-BI–mediated efflux to discoidal HDL particles composed of apo AI molecules with 2 different double-point mutations was dramatically reduced, but there was no decrease in high-affinity binding to SR-BI relative to particles containing wild-type apo AI. Interestingly, efflux was restored to the HDL particles containing the mutant apo AI molecules when SR-BI was also mutated. These observations are consistent with a “productive complex” mechanism whereby both SR-BI and the acceptor must either be correctly aligned or have the ability to undergo appropriate conformational changes for there to be efficient FC efflux.33 Such a mechanism is also thought to apply to the selective uptake of acceptor lipids by SR-BI.22 For example, similarly to apo AI–containing particles, apo E particles exhibit high-affinity binding to SR-BI, yet selective uptake of cholesteryl ester via SR-BI is less efficient compared with that from apo AI particles. Finally, it should be noted that regardless of the mechanism of the binding-dependent component of SR-BI–mediated FC efflux, the cholesterol-rich domains associated with SR-BI might be expected to contribute to the facilitation
in efflux by providing a larger FC pool that is available for transfer.

**ABCA1-Mediated FC Efflux**

Early studies demonstrated that some cells, in particular cholesterol-enriched macrophages, would release both FC and phospholipid to lipid-free apolipoproteins.\(^{34-36}\) Later studies showed that cholesterol-enriched fibroblasts and macrophages from patients with Tangier disease lacked the ability to release both phospholipid and FC to lipid-free apolipoproteins but that efflux to mature HDL was normal.\(^{37,38}\) Recent studies have shown that the genetic defect responsible for Tangier disease is attributable to mutations in ABCA1.\(^{39-42}\) Individuals with Tangier disease have almost no HDL cholesterol, and their apo AI remains poorly lipidated and is rapidly catabolized.\(^{43}\) Thus, in mediating the efflux of FC and phospholipid from cells, ABCA1 also mediates the lipidation of apo AI and the formation of nascent HDL. In contrast to aqueous diffusion and SR-BI–mediated FC flux, the movement of FC by ABCA1 is unidirectional and net efflux of cellular FC would always occur via this mechanism.

ABCA1 is a member of a large family of ATP-binding cassette transporters that have common structural motifs and use ATP as an energy source to transport a variety of substrates, including ions, lipids, and cytotoxins.\(^{44}\) The ABCA1 molecule can be divided into halves, with each half having a transmembrane domain containing 6 helices and an extracellular domain with a large extracellular loop.\(^{45}\) Recent studies have shown that the genetic defect responsible for Tangier disease is attributable to mutations in ABCA1.\(^{39-42}\) Several models of ABCA1-mediated efflux have been proposed,\(^{62-64}\) but it is unclear, however, whether this recycling plays a role in ABCA1-mediated lipid efflux or if it functions in ABCA1 degradation.\(^{49}\) At the plasma membrane, ABCA1 is associated with modified domains that are distinct from sphingomyelin-rich lipid rafts and caveolae.\(^{50}\) and recent studies have shown that ABCA1 may be associated with domains that are enriched in cholesterol and unsaturated fatty acid–enriched PC.\(^{51}\)

ABCA1 expression is regulated by a variety of mechanisms (for a detailed review, see the article by Oram in this series). Briefly, the transcription of ABCA1 is induced by nuclear orphan receptors, liver X receptors (LXR) \(\alpha\) or \(\beta\), and retinoid X receptor (RXR), alone or in combination, in which case, the effect is additive.\(^{52}\) Oxyesters, including 27-, 22(R)-, and 20(S)-hydroxycholesterol,\(^{52-54}\) potent ligands of the LXR, whereas 9-cis-retinoic acid is an effective RXR activator.\(^{55}\) The upregulation seen with cholesterol enrichment of cells is also probably mediated by the LXR/RXR system.\(^{52,54}\) ABCA1 transcription is also stimulated in some macrophages by cAMP.\(^{55}\) Posttranscriptional regulation of ABCA1 is afforded by apo AI binding, which stabilizes the receptor and prevents its degradation,\(^{56}\) whereas unsaturated fatty acids seem to promote its turnover.\(^{59}\)

In contrast to SR-BI–mediated FC efflux, the preferred cholesterol acceptor for ABCA1 is lipid-poor apolipoproteins. All of the exchangeable apolipoproteins, such as apo AI, apo AII, apo AIV, apo E, and apo C, can act as phospholipid and cholesterol acceptors for ABCA1.\(^{55,57}\) In some instances, efflux to HDL, preparations via ABCA1 has been documented\(^{55}\); however, it is our experience that this effect is variable and is most likely attributable to the amount of dissociated apolipoprotein in the preparation (Rothblat, unpublished data). Amphipathic \(\alpha\)-helices are the motif involved in efflux, because insect apolipophorin III \(^{58}\) and synthetic peptides containing amphipathic helices\(^{59,59}\) can also act as acceptors. Mutations affecting the C-terminal domain of apo AI, thereby reducing its lipid affinity, also impair efflux.\(^{60-62}\)

Several studies suggest that a direct interaction of the transporter and apolipoprotein plays a role in ABCA1-mediated efflux (Figure 2). ABCA1 has been shown to cross-link with apo AI, indicating a very close association between the 2 proteins.\(^{63-65}\) In addition, recent studies by Fitzgerald et al\(^{47}\) showed that 4 different mutant ABCA1 transporters with naturally occurring missense mutations in the large extracellular domains exhibited little or no apo AI–induced efflux or cross-linking to apo AI. This suggests that a direct interaction between apo AI and ABCA1 is required for efflux. Interestingly, a fifth ABCA1 mutant retained cross-linking to apo AI but was defective at mediating efflux, suggesting that there are other requirements for effective efflux. An alternative model is that the apolipoproteins interact with a lipid domain that is formed by a functional ABCA1 (Figure 2). This model is supported by data showing that an intact ABCA1 ATPase activity is necessary for apolipoprotein binding to the cell surface.\(^{66}\) In addition, ABCA1 expression changes membrane morphology,\(^{65,67}\) suggesting that there is an increased quantity of phospholipid and cholesterol in the outer leaflet of the plasma membrane. Furthermore, recent studies showed that the cholesterol released via ABCA1 is associated with PC and cholesterol-enriched domains.\(^{61}\) In addition, recent studies showed that point mutations in helix 10 of apo AI reduced ABCA1-mediated cholesterol efflux and that the lipid-binding characteristics of the various mutant apo AI molecules were positively correlated with ABCA1-mediated FC efflux.\(^{62}\) Interestingly, ABCA1-mediated efflux was not affected when helices other than helix 10 of apo AI were mutated.\(^{62}\) Taken together, the data suggest that an interaction of apo AI with both lipid domains and ABCA1 is required for efflux (Figure 2). Thus, a hybrid model has been proposed in which helix 10 of apo AI initially tethers the apolipoprotein to an ABCA1-generated lipid domain.\(^{62}\) The apo AI then diffuses laterally in the membrane, where it forms a productive complex with ABCA1, leading to the lipidation of the apolipoprotein and the formation of nascent HDL.\(^{62}\) Consistent with such a concept is that there is no measurable cross-linking of ABCA1 and apo AI at 4°C, raising the possibility that changes in membrane fluidity at lower temperatures prevent the insertion of apo AI into the lipid bilayer and the subsequent direct interaction of apo AI with ABCA1.\(^{47}\)

Several models of ABCA1-mediated efflux of phospholipid and cholesterol to apolipoproteins have been proposed,
including molecular efflux (“two-step” or “sequential” model), in which individual molecules of phospholipid are transferred to apolipoproteins followed by acquisition of cholesterol, and membrane solubilization (“one-step” model), in which phospholipid and cholesterol are mobilized simultaneously as discrete units, either small (microsolubilization) or large (macrosolubilization) (Figure 3). These models remain the subject of intense study by many groups.

According to the sequential model, ABCA1 first promotes the lipidation of apolipoproteins with phospholipid, generating the classic pre-β, phospholipid-rich particles thought to be nascent HDL. These particles would then be capable of acquiring cholesterol secondarily from other membrane domains. Uncoupling of phospholipid and cholesterol efflux has been accomplished by several approaches, such as depleting plasma membrane cholesterol with cyclodextrin, affecting cholesterol trafficking to the membrane, and inhibiting protein kinase C. Other evidence in support of this model comes from studies of multiple-cell systems in which phospholipid-rich conditioned media is incubated with cholesterol donor cells and studies with smooth muscle cells that exhibit phospholipid efflux while cholesterol efflux appears to be impaired. However, there is no convincing

Figure 2. Proposed models for ABCA1-mediated lipid efflux to apolipoprotein A1. A, Apo AI binds directly to ABCA1 and acquires both phospholipid and cholesterol to form a nascent HDL. B, Apo AI interacts with a specialized lipid domain associated with ABCA1 and is subsequently lipidated. C, Helix 10 of Apo AI tethers the apolipoprotein to a specialized lipid domain associated with ABCA1. Apo AI diffuses laterally along the bilayer and complexes with ABCA1, leading to the production of nascent HDL.

Figure 3. Models of ABCA1-mediated efflux of cholesterol and phospholipid to apolipoproteins. A, Molecular efflux. An apolipoprotein acquires individual molecules of phospholipid. The phospholipid-rich apolipoprotein then acquires cholesterol. B, Membrane solubilization. Phospholipid and cholesterol are acquired simultaneously by an apolipoprotein as small (microsolubilization) or large (macrosolubilization) units of plasma membrane. See text for additional details.
kinetic data that phospholipid and cholesterol are transferred separately, and the studies discussed above, in which cholesterol and phospholipid efflux are uncoupled, do not differentiate between the molecular and membrane solubilization models of ABCA1-mediated lipid efflux.

The simultaneous mechanism contends that phospholipid and cholesterol are released together. Thus, solubilization of membrane units is linked to ABCA1-apo AI–induced membrane vesiculation, resulting in the release of both cholesterol and phospholipid en masse. Support for this mechanism comes from several different studies. The kinetics of phospholipid and cholesterol efflux parallel one another, giving similar initial rates of release in the first 10 minutes of efflux. In addition, efflux from cells, particularly cholesterol-enriched cells, results in molar ratios of cholesterol and phospholipid >2.5; this value is higher than what would be expected if phospholipid was released first and FC subsequently acquired, because the equilibrium solubility of cholesterol in phospholipid bilayers is equimolar. Another model of simultaneous efflux, retroendocytosis, suggests that ABCA1 facilitates the intracellular lipidation of apolipoproteins and resecretion of nascent HDL particles.

Another possibility worth considering is that both the molecular and simultaneous release mechanisms exist but have very different physiological functions. Thus, in hepatocytes, the molecular release of lipids would result in the production of nascent HDL particles that subsequently evolve into mature HDL. In contrast, ABCA1-mediated membrane solubilization occurring in macrophage foam cells within the vessel wall would be an efficient vehicle for the removal of excess cell cholesterol without sacrificing large amounts of membrane phospholipid. Such a pathway could explain the presence of FC-rich particles often isolated from atherosclerotic plaque.

Overview

Both ABCA1 and SR-BI play important roles in the formation and metabolism of serum lipoproteins as well as in the maintenance of cell cholesterol homeostasis. As our knowledge of these two proteins increases, it is becoming clear that there are several interrelated metabolic steps that link these proteins, both in terms of cellular lipid metabolism and the ligands in serum that participate in reverse cholesterol transport. Only one detailed study has been done on the impact of expression of both proteins in a cell. Thus, the studies by Chen et al. demonstrated that the expression of SR-BI resulted in a reduction in ABCA1-mediated efflux of cholesterol but not phospholipid. These authors proposed that SR-BI expression produced a reuptake pathway in which cholesterol released from the cell to apolipoproteins by ABCA1 was incorporated back into the cell by SR-BI–mediated influx. Another possibility is that SR-BI, which has been shown to reorganize membrane lipids, sequesters cholesterol, making it unavailable for ABCA1 efflux. This competition between the two proteins could have far-reaching implications, both in terms of cell cholesterol homeostasis, where this cycle could result in the retention of cell cholesterol, and by influencing the composition of the nascent particles formed by ABCA1. Reuptake or sequestering of cholesterol by SR-BI could produce a phospholipid-rich nascent lipoprotein that would function as an efficient acceptor of cholesterol from other cells and represent a precursor to mature HDL.

Other relationships between SR-BI and ABCA1 can be seen with regard to the ligands in serum with which they interact. As described above, lipid-poor apolipoproteins are the preferred substrate for ABCA1-mediated lipidation, whereas mature, phospholipid-rich particles serve as the best acceptors of cell cholesterol delivered by SR-BI. The remodeling of lipoproteins by serum enzymes and transfer proteins produces shifts in lipoprotein surface and core lipids that affect the distribution of exchangeable apolipoproteins between those bound to HDL and VLDL and apolipoproteins unassociated with lipoproteins. This distribution of apolipoproteins would influence the relative ABCA1 and SR-BI efflux efficiency of serum, with ABCA1-mediated efflux being enhanced by dissociation of apolipoproteins from lipoprotein particles.

Finally, the obvious question is what are the roles of ABCA1 and SR-BI are in reverse cholesterol transport and the development of atherosclerosis. Unfortunately, there is no complete answer at this stage. The two sites of primary interest are the cells in the vessel wall; particular macrophage-derived foam cells, and the liver. ABCA1 and SR-BI are expressed at both of these locations; thus, further studies of the interrelationships between these proteins and the ligands with which they interact are of major importance. Although ABCA1 is clearly linked to the production of HDL, it also seems to function in eliminating excess cholesterol from cells and in maintaining cell cholesterol homeostasis (Bortnick and Rothblat, unpublished observations). On this basis, ABCA1 is expected to serve an antiatherogenic function. In humans, there is an association between increased arterial-wall thickness and impaired ABCA1-mediated FC efflux. In addition, transplantation of ABCA1 mice bone marrow into apo E mice accelerated atherosclerosis development. The role of SR-BI in RCT is more complex because it can function both as a cholesterol donor and acceptor. The contribution of the selective cholesteryl ester uptake process and the bidirectional flux of FC to net cholesterol movement between cells and lipoproteins remains to be established. In the liver, SR-BI clearly seems to serve a cholesterol delivery function. In the vessel wall, the contribution of SR-BI to cholesterol movement is more elusive, and its role in net cholesterol flux will depend on the cholesterol status of the cells as well as the composition and concentration of the lipoproteins and apolipoproteins in the extracellular environment. Nonetheless, in rodents, at least, SR-BI seems to serve an antiatherogenic function.

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