HDL Apolipoproteins and ABCA1
Partners in the Removal of Excess Cellular Cholesterol

John F. Oram

Abstract—It is widely believed that HDL protects against atherosclerosis by removing excess cholesterol from arterial cells. Lipid-poor HDL apolipoproteins promote efflux of cholesterol, phospholipids, and other lipophilic molecules from cells by an active process mediated by a cell-membrane transporter called the ATP binding cassette transporter A-1 (ABCA1). ABCA1 either directly or indirectly translocates phospholipids and cholesterol to the cell surface, where they appear to form lipid domains that interact with amphipathic α-helices in apolipoproteins. This interaction solubilizes these lipids and generates nascent HDL particles that dissociate from the cell. Binding of apolipoproteins to ABCA1 may also enhance the activity of this lipid-transport pathway. Thus, the apolipoprotein/ABCA1 pathway efficiently clears cells of excess cholesterol that would otherwise accumulate as intracellular lipid droplets. ABCA1 expression is highly induced by cholesterol loading of cells and is also modulated by sterol-independent mechanisms at both the transcriptional and posttranslational level. Studies of human disease and animal models have shown that both an increased availability of apolipoproteins and an enhanced macrophage ABCA1 activity are atheroprotective. These findings implicate the apolipoprotein/ABCA1 pathway as an important therapeutic target for treating cardiovascular disease. (Arterioscler Thromb Vasc Biol. 2003;23:720-727.)

Key Words: HDL ■ apolipoproteins ■ ABCA1 ■ cholesterol efflux ■ cardiovascular disease

Population studies have consistently shown an inverse relation between plasma HDL levels and risk for cardiovascular disease, implying that factors associated with HDL are atheroprotective. Although some of this protection may be related to the antioxidative and anti-inflammatory effects of HDL, it is widely believed that HDL components inhibit atherosclerotic lesion formation by removing excess cholesterol from arterial cells.

Cell culture experiments revealed that HDL components remove cellular cholesterol by multiple mechanisms. HDL phospholipids absorb cholesterol that diffuses from the plasma membrane, a passive process that is facilitated by the interaction of HDL particles with scavenger receptor B1 (SR-B1). In contrast, HDL apolipoproteins remove cellular cholesterol, phospholipids, and other metabolites by a regulated, active-transport process mediated by a cell membrane protein called ATP binding cassette transporter A1 (ABCA1).

Although ABCA1 was identified as a lipid transporter only recently, its existence was predicted 2 decades ago when it was proposed that HDL promotes cholesterol efflux from cells through its interaction with a cholesterol-inducible receptor. These and subsequent studies have provided a great deal of insight into the mechanisms by which apolipoproteins interact with cells and remove lipids. The present review focuses on the properties of the apolipoprotein-mediated lipid-removal pathway and how these relate to the cell biology of ABCA1.

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Structure and Function of ABCA1

The role of ABCA1 as an exporter of cellular lipids became evident when it was discovered that it was the gene product defective in Tangier disease, a severe HDL deficiency characterized by deposition of sterols in tissue macrophages. Cells isolated from Tangier disease homozygotes were shown to have a severely impaired ability to transport cholesterol and phospholipids to purified apolipoproteins. ABCA1 is a 2261-amino acid integral membrane protein that is a member of a superfamily of ABC transporters that utilize ATP as a source of energy for transporting lipids and other metabolites across membranes. ABCA1 comprises 2 halves of similar structure that are linked covalently. Each half has a nucleotide-binding domain (NBD) containing 2 conserved peptide motifs known as Walker A and Walker B, which are present in many proteins that utilize ATP, and a transmembrane domain containing six helixes (Figure 1). ABCA1 is predicted to have an N-terminus oriented into the cytosol and 2 large extracellular loops that are highly glycosylated and linked by 1 or more cysteine bonds (Figure 1).

ABCA1 either directly or indirectly mediates transport of cholesterol and phospholipids across cellular membranes, where they are removed from cells by apolipoproteins. Its homology with other better-characterized ABC transporters suggests that ABCA1 may form a channel in the membrane that promotes “flopping” of lipids from the inner to the outer membrane leaflet by an ATPase-dependent process. Examples of this class of ABCs are members of the multidrug resistant transporter family. One study, however, provided evidence that the ATPase activity in ABCA1 is not actually involved in lipid transport, consistent with ABCA1’s functioning as a regulator rather than an active transporter. Examples of this class of ABCs are the cystic fibrosis transmembrane conductance regulator and sulfonamide receptor 1. These ATPase experiments should be interpreted with caution, however, as ABCA1 was expressed in insect cells, where it may not function normally. ABCA1 localizes to the plasma membrane and intracellular compartments, where it could potentially facilitate transport of lipids to either cell surface-bound or internalized apolipoproteins.

ABCA1 appears to target specific membrane domains for lipid secretion. These are likely to be regions that are sensitive to overaccumulation of cholesterol and other lipophilic compounds. This same source of cholesterol feeds into intracellular compartments that are the preferred substrate for the esterifying enzyme, acyl CoA:cholesterol acyltransferase (ACAT). Thus, ABCA1 removes cholesterol that would otherwise accumulate as cytosolic cholesteryl-ester lipid droplets. One possibility is that both ABCA1 and ACAT function to protect cells from incorporating too much free cholesterol into the endoplasmic reticulum, where it may disrupt the peptide biosynthetic machinery. Two models have been proposed to account for the ability of ABCA1 to target specific lipid domains. The exocytosis model implies that excess intracellular cholesterol is packaged into transport vesicles, or rafts, perhaps in the Golgi apparatus, which translocate to domains in the plasma membrane containing ABCA1. These cholesterol-rich domains can also be generated in the plasma membrane by exposing cells to free cholesterol. The retroendocytosis model suggests that ABCA1- and apolipoprotein-containing vesicles endocytose to intracellular lipid deposits, where ABCA1 mediates lipid transport into the vesicle lumen for release by exocytosis. ABCA1 has been shown to recycle rapidly between the plasma membrane and late endosomal/lysosomal compartments, consistent with this second mechanism. This rapid recycling, however, may function to regulate ABCA1 degradation rather than lipid transport, as ABCA1 has a rapid rate of turnover in macrophage cell lines.

ABCA1 may form a complex with other proteins that modulate its intracellular trafficking. The carboxy terminus has been reported to interact with β2-syntrophin and utrophin in macrophages, forming a protein complex that might couple ABCA1 to the cytoskeleton. In addition, the relative expression of ABCA1 was shown to alter the level of GTP-binding proteins of the Rho family that modulate cytoskeletal structure and protein interactions. This may reflect the involvement of vesicular transport pathways required for ABCA1-mediated lipid trafficking or targeting of ABCA1 to lipid domains. ABCA1 is selectively expressed on
the basolateral membranes of cultured intestinal, gall bladder epithelial, brain capillary endothelial, and hepatic cells, indicating the presence of factors that target ABCA1 to specific membranes in polarized cells.

ABCA1 appears to mediate transport of diverse types of molecules. In addition to cholesterol and phospholipids, ABCA1 has been reported to promote secretion of \( \alpha \)-tocopherol, apolipoprotein (apo) E, and interleukin-1\( \beta \). ABCA1-mediated secretion of \( \alpha \)-tocopherol mimics that of cholesterol, suggesting similar transport mechanisms for these substrates.

ABCA1 can promote phospholipid efflux from cells even when membranes are depleted of cholesterol, consistent with phospholipids being the primary substrate for ABCA1. This assumption is supported by data showing that ABCA1 does not directly bind cholesterol. Analysis of lipids removed by apolipoproteins implicates phosphatidylcholine as the major phospholipid substrate. There is evidence that ABCA1 translocates phosphatidylserine (PS) to the exofacial side of the plasma membrane, a process proposed to account for ABCA1-mediated cellular apoA-I binding and cholesterol efflux. Another study, however, showed that the increased PS translocation associated with induction of ABCA1 was too small to account for the enhanced apoA-I binding and cholesterol efflux. Moreover, there is no selective enrichment of PS in the phospholipids removed by apolipoproteins, suggesting little interaction with PS-rich domains. A problem with interpreting the physiological relevance of these findings is that PS translocation is a symptom of damaged cells, which may occur if ABCA1 is overexpressed for too long.

The broad substrate specificity of ABCA1 conforms to the targeted lipid-domain hypothesis. It is possible that ABCA1 can simultaneously transport several molecules, provided they are associated with phosphatidylcholine. These could include cholesterol and other lipophiles (eg, \( \alpha \)-tocopherol or peptides) that accumulate in membrane domains accessible to ABCA1. Alternatively, if ABCA1 acts as a regulator rather than a direct transporter, it could mediate the translocation and plasma membrane fusion of transport vesicles or rafts enriched in these components. Although ABCA1 may mediate transport of diverse types of molecules, the most physiologically relevant of these substrates are likely to be cholesterol and phospholipids, because overloading cells with cholesterol induces ABCA1 expression (see below), and phospholipids are required cofactors for cholesterol transport.

**Apolipoprotein-Mediated Removal of Cellular Lipids**

HDL apolipoproteins selectively interact with plasma-membrane lipid domains that are formed by the action of ABCA1. This interaction is specific for apolipoproteins that contain no or very little lipid. This was evident from studies showing that purified HDL apolipoproteins promote cholesterol and phospholipid efflux from cells exclusively by this pathway. In contrast, lipidated apolipoproteins, such as mature HDL particles, promote cholesterol efflux by both the ABCA1 pathway and passive diffusion. Whether or not an HDL particle has activity for the ABCA1 pathway may depend on its ability to act as a donor of lipid-free apolipoproteins that dissociate from the particles. This concept is supported by studies showing that light trypsinization of HDL under conditions that digest only 10% of the apolipoproteins can completely abolish the ability of these particles to remove cellular cholesterol by the ABCA1 pathway. It is likely that these highly trypsin-sensitive apolipoproteins are those that can freely exchange between HDL particles and the cell membrane.

This lipid-transport pathway has broad specificity for multiple exchangeable apolipoproteins, including apoa I, AII, E, C, and AIV. These apolipoproteins contain 11 to 22 amino acid repeats of amphipathic \( \alpha \)-helices. In this type of helix, the charged amino acids align along 1 face of the long axis while the hydrophobic residues align along the other face. The amphipathic \( \alpha \)-helices in exchangeable apolipopro-
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Figure 3. Model for the apolipoprotein/ABCA1 lipid-removal pathway. Excess cholesterol is incorporated into phospholipid domains of the inner leaflet of the plasma membrane. ABCA1 transports cholesterol and phospholipids into its transmembrane chamber, where they are "flipped" to the outer leaflet of the plasma membrane and extruded from the chamber. Lipid-poor apoA-I solubilizes these cell-surface lipid domains, forming disc-shaped, nascent HDL particles.

How apolipoproteins remove cellular cholesterol is still being debated. Several studies have suggested that apolipoproteins simultaneously remove both phospholipids and cholesterol from cellular membranes by a microsolubilization process. Other studies have suggested that apolipoproteins first remove phospholipids by an ABCA1-dependent process and then acquire cholesterol by diffusional mechanisms. Both of these models assume that apolipoproteins interact with lipid microdomains within membranes, presumably formed by the action of ABCA1. The properties of these domains are unknown, but they appear to be separate from sphingolipid-rich rafts and caveolae. A fraction of ABCA1, however, may associate with membrane rafts that are selectively solubilized by the detergent Lubrol and are relatively enriched with cholesterol and phosphatidylcholine. Immunogold electron microscopy showed that apoA-I and apoE interact with diffuse structures protruding from the plasma membrane. It is likely that these structures are formed by the lipid-transport activity of ABCA1, as has been shown for another ABC phospholipid transporter.

The apparent discrepancies between the microsolubilization and 2-step models may reflect differences in methodology that affect the lipid composition of membrane lipid domains. Under physiological conditions, the ABCA1 pathway is likely to be active only when these domains are cholesterol rich, as excess sterols are required for induction of ABCA1 gene expression. Thus, solubilization of these domains by apolipoproteins is likely to remove both phospholipid and cholesterol. Indeed, the lipids removed by apoA-I from cholesterol-loaded fibroblasts are cholesterol enriched when compared with the average membrane composition. When ABCA1 is forcibly overexpressed in cells, however, the membrane domains formed by ABCA1 may be relatively depleted of cholesterol. In this case, apolipoproteins would remove largely phospholipid and promote cholesterol efflux from other membrane domains by diffusional mechanisms.

The x-ray crystal structure of a bacterial ABC lipid transporter suggests a possible model for the apolipoprotein/ABCA1 pathway (Figure 3). Excess cellular cholesterol may accumulate within domains of the cytoplasmic leaflet of the plasma membrane, where cholesterol tends to distribute. This cholesterol is not accessible to apolipoproteins and therefore must be translocated to the cell surface for removal.

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These lipid domains may assemble in the vicinity of ABCA1 molecules, or ABCA1 may migrate to these domains after they are formed. The model predicts that the 2 transmembrane bundles form half-cylinders that are initially closed at the outer leaflet but are spread open at the inner leaflet, allowing ABCA1 to “scoop up” lipids selectively from the cytoplasmic side. The interactions of lipids and ATP with ABCA1 cause the half-cylinders to close, forming a chamber that “flips” the trapped lipids to the outer leaflet through the interactions of polar head groups with charged amino acids. The chamber then opens at the outer leaflet, extruding its lipid content. ApoA-I interacts with the cell-surface lipid domains formed by this process, solubilizing lipids and forming nascent disc-shaped HDL particles. It is predicted that each disc contains 2 apoA-I molecules wrapped around the edge like parallel belts. Although this model explains much of the existing data, its verification requires more information about ABCA1 structure and its lipid translocase activity.

Apolipoprotein-ABCA1 Interactions

There is mounting evidence that apolipoproteins interact directly with ABCA1. Cross-linking studies revealed that cell surface–bound apoA-I comes within 1.2 nm of ABCA1. The apparent molecular mass of the cross-linked species is consistent with only 1 molecule of apoA-I bound per molecule of ABCA1. Cross-linking activity is temperature sensitive and occurs when both lipid- and water-soluble cross-linking agents are used, raising the possibility that apoA-I interacts with ABCA1 in both the aqueous and lipid environments.

Studies of ABCA1 and apoA-I mutants have not yet presented a clear picture of the properties of this interaction. Some naturally occurring point mutations in the extracellular loops of ABCA1 severely impair both the lipid transport and apoA-I cross-linking activities of ABCA1. This suggests that the interactions of apoA-I with key residues in these loops are important for mediating lipid efflux. A mutation in the first intracellular ATP binding domain, however, also appears to impair apoA-I binding to ABCA1-expressing cells. Not all loss-of-function mutations in ABCA1 reduce apoA-I cross-linking, as substitution of tryptophan for serine in residue 590 of the first extracellular loop markedly decreases cholesterol efflux without affecting apoA-I cross-linking activity. These studies imply that binding of apoA-I to ABCA1 may be necessary but not sufficient for stimulating cholesterol efflux.

It is also unclear what role lipid interactions play in the binding of apolipoproteins to ABCA1. One report showed that the diffusional parameters of membrane-bound apoA-I were consistent with lipid interactions, whereas another study, using fluorescent photobleaching, suggested that apoA-I binding to ABCA1-expressing cells was relatively immobile, more consistent with direct protein interactions. Studies with apoA-I mutants, where α-helical segments were exchanged, revealed a close but not absolute relation between apolipoprotein affinity for phospholipids and ability to promote cholesterol efflux by the ABCA1 pathway. This apparent complexity of apoA-I interactions with ABCA1-expressing cells may be because apolipoproteins interact both with ABCA1 and the lipid domains formed by ABCA1, and these interactions depend on different molecular properties.

Binding of apolipoproteins to ABCA1 is likely to play 1 or more important roles in mediating lipid transport, and there are several possibilities. First, it may serve to target apolipoproteins to lipid domains formed by ABCA1 and facilitate the assembly of apolipoprotein/lipid particles. Second, apolipoprotein binding may stabilize ABCA1, increasing its membrane content and enhancing lipid efflux. In support of this idea is a study showing that incubating cells with apolipoproteins inhibits proteolytic degradation of ABCA1 protein. Lastly, binding of apolipoproteins to ABCA1 may activate intracellular signaling pathways that modulate lipid trafficking. Multiple studies over the last decade have provided evidence that the interaction of lipid-free apoA-I with cells elicits signals, which involve activation of phospholipases and protein kinase C. More recent studies have shown that the activity or cellular content of ABCA1 influences signaling pathways. There are still no data, however, establishing a direct link between apolipoprotein binding to ABCA1 and any of these processes.

Regulation of ABCA1

As expected for a transporter that mediates secretion of excess cellular cholesterol, transcription of ABCA1 is markedly induced by overloading cells with cholesterol. This induction occurs exclusively through activation of the nuclear receptors liver X receptor (LXRα and/or LXRβ) and retinoid X receptor (RXR). LXR and RXR form obligate heterodimers that preferentially bind to response elements within the ABCA1 gene promoter and the first intron. LXRs and RXRs bind to and are activated by oxysterols and retinoic acid, respectively. Binding of either 1 or both ligands can activate transcription. Treatment of cells with either an oxysterol or 9-cis-retinoic acid induces ABCA1, but their combined treatment has marked synergistic effects. The LXRα gene promoter in human macrophages contains an LXR-response element, indicating that LXRs can auto-regulate its own expression. This would serve to amplify the effects of oxysterols on the ABCA1 lipid-efflux pathway.

Because uptake of nonoxidized cholesterol by cells increases ABCA1 expression, cholesterol must be converted to oxysterols before inducing ABCA1. Oxysterols therefore act like second messengers for signaling a build-up of excess membrane cholesterol. The most potent LXR ligands contain a single stereoselective oxygen on the side chain that functions as a hydrogen bond acceptor. Many of these oxysterols are generated by cytochrome P450 enzymes that are particularly prevalent in the liver and play a role in bile acid metabolism. It is believed that 22-hydroxycholesterol, 24-hydroxycholesterol, and 24,25-epoxycholesterol are the major, naturally occurring liver LXR ligands. One of these enzymes, sterol 27-hydroxylase (Cyp27), is broadly distributed in various tissues and cell types, including macrophages, suggesting that 27-hydroxycholesterol is the major LXR ligand in macrophages and other peripheral cells. Consistent with this idea is the accelerated atherosclerosis that is associated with cerebrotendinous xanthomatosis, a rare inherited disease characterized by a lack of Cyp27. Recent
Regulation of ABCA1 Expression

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ggPP indicates geranylgeranyl pyrophosphate; IFN, interferon; TGF, transforming growth factor; FAs, fatty acids.

Concluding Remarks

ABCA1 plays a critical role in mediating efflux of cellular cholesterol, phospholipids, and other molecules to lipid-poor apolipoproteins. ABCA1 expression in cells is highly regulated by transcriptional and posttranscriptional mechanisms. ABCA1 is unique among ABC transporters in that it requires an apolipoprotein partner for transporting substrates. These apolipoproteins not only act as acceptors for the transported lipids but they may also enhance the activity of the pathway through their direct interactions with ABCA1. Studies of human disease and animal models have shown that modulating both apolipoprotein supply and ABCA1 activity affects atherogenesis. Thus, the apolipoprotein/ABCA1 pathway has become an important target for therapeutic interventions designed to prevent cardiovascular disease.

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References


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