Signal Transduction by HDL: Agonists, Receptors, and Signaling Cascades

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Contents

Abstract

Numerous epidemiologic studies revealed that high-density lipoprotein (HDL) is an important risk factor for coronary heart disease. There are several well-documented HDL functions such as reversed cholesterol transport, inhibition of inflammation, or inhibition of platelet activation that may account for the atheroprotective effects of this lipoprotein. Mechanistically, these functions are carried out by a direct interaction of HDL particle or its components with receptors localized on the cell surface followed by generation of intracellular signals. Several HDL-associated receptor ligands such as apolipoprotein A-I (apoA-I) or sphingosine-1-phosphate (S1P) have been identified in addition to HDL holoparticles, which interact with surface receptors such as ATP-binding cassette transporter A1 (ABCA1); S1P receptor types 1, 2, and 3 (S1P$_1$, S1P$_2$, and S1P$_3$); or scavenger receptor type I (SR-BI) and activate intracellular

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signaling cascades encompassing kinases, phospholipases, trimeric and small G-proteins, and cytoskeletal proteins such as actin or junctional protein such as connexin43. In addition, depletion of plasma cell cholesterol mediated by ABCA1, ATP-binding cassette transporter G1 (ABCG1), or SR-BI was demonstrated to indirectly inhibit signaling over proinflammatory or proliferation-stimulating receptors such as Toll-like or growth factor receptors. The present review summarizes the current knowledge regarding the HDL-induced signal transduction and its relevance to athero- and cardioprotective effects as well as other physiological effects exerted by HDL.

Keywords

High-density lipoprotein (HDL) • Apolipoprotein A-I (apoA-I) • ATP-binding cassette transporter A1 (ABCA1) • Scavenger receptor type I (SR-BI) • Sphingosine-1-phosphate (S1P) • Signal transduction

Abbreviations

ABCA1	ATP-binding cassette transporter A1
ABCG1	ATP-binding cassette transporter G1
AMPK	AMP-activated protein kinase
Apo	Apolipoprotein
CAMK	Calcium/calmodulin-dependent protein kinase
cAMP	Cyclic adenosine monophosphate
Cdc42	Cell division control protein 42
CHD	Coronary heart disease
CKD	Chronic kidney disease
COX-2	Cyclooxygenase-2
DAG	diacylglycerol
DHEA	Dehydroepiandrosterone
EL	Endothelial lipase
eNOS	Endothelial nitric oxide synthase
GLUT4	Glucose transporter type 4
GM-CSF	Granulocyte macrophage colony-stimulating factor
HDL	High-density lipoprotein
HSPC	Hematopoietic stem progenitor cells
IL	Interleukin
JAK2	Janus kinase 2
JNK	c-Jun N-terminal kinase
LCAT	Lecithin:cholesterol acyltransferase
LDL	Low-density lipoprotein

LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCP1	Monocyte chemotactic protein 1
MDCK	Madin-Darby canine kidney
PC	Phosphatidylcholine
PC-PLC	PC-specific phospholipase C
PC-PLD	PC-specific phospholipase D
PDZK1	PDZ domain-containing adaptor protein
PGI_2	Prostacyclin
PHD	Prolyl hydroxylase
PI3K	Phosphatidylinositol 3-kinase
PI-PLC	Phosphatidylinositol-specific phospholipase C
PKA	Protein kinase A
PKC	Protein kinase C
S1P	Sphingosine-1-phosphate
SAA	Serum amyloid A
SDMA	Symmetric dimethylarginine
SK	Sphingosine kinase
SPC	Sphingosylphosphorylcholine
SPM	Sphingomyelin
SR-BI	Scavenger receptor type I
STAT3	Signal transducer and activator of transcription 3
TGFβ	Transforming growth factor-β
TLR	Toll-like receptor
TNFα	Tumor necrosis factor α
β-ATPase	F1F0 ATP synthase β-subunit

1   Introduction

Innumerable epidemiological studies document the inverse relationship between plasma levels of high-density lipoprotein (HDL) cholesterol and cardiovascular risk. The first hypothesis aiming to mechanistically explain this relationship has been formulated by John Glomset (1968), who proposed that HDL particles take up excess cholesterol in peripheral tissues including atherosclerotically changed arterial walls and transport it to the liver for excretion with bile. The first step in this process termed reverse cholesterol transport encompassed direct interaction between HDL and cell membrane with the subsequent efflux of cholesterol to lipoprotein particles. Early concepts envisioned cholesterol efflux as a purely physicochemical phenomenon with the unidirectional flux of free cholesterol perpetuated by a steady concentration gradient maintained by the activity of lecithin:cholesterol acyltransferase (LCAT) in HDL particles. John F. Oram was the first to note that HDL binding to specific binding sites precedes cholesterol

efflux and is required for the effective mobilization of free cholesterol from internal pools and its transport to the plasma membrane, where it is available for further transfer to lipoprotein particles (Graham and Oram 1987; Slotte et al. 1987). The seminal discovery of Oram put HDL function in a fully new perspective: ever since then HDL has been perceived not only as a cholesterol transporter but also as hormone-like particle exerting its activities through binding to specific receptors.

Signal transduction occurs when an extracellular signaling molecule activates a surface receptor, which in turn alters intracellular molecules creating a response, which ultimately modifies cellular functions. The recognition of specific HDL binding sites raised immediately a question, whether HDL-cell interaction is linked to signaling events relevant to intracellular cholesterol transport and/or cholesterol efflux. It was Oram again who demonstrated that the exposure of fibroblasts to HDL causes activation of protein kinase C (PKC), which in turn contributes to translocation of free cholesterol between intracellular membranes and plasmalemma (Mendez et al. 1991). This finding opened a new field of research focusing on dissection of intracellular signaling pathways that are induced by HDL or its constituents and mediate cellular responses to lipoprotein particles. In the following years, several ligands present in HDL and their receptors expressed on the cell surface could be identified that mediate one or more physiological effects attributed to this lipoprotein. In addition, the interaction of HDL with the cell membrane was found to potently modify signal transduction induced by other ligands such as pathogen-associated molecular patterns (PAMPs) or growth factors. This review attempts to summarize the current state of knowledge on HDL-induced signal transduction and its physiological relevance.

2   ApoA-I-Induced Cell Signaling Directly Mediated by ABCA1

ATP-binding cassette transporter A1 (ABCA1) has been originally identified as a protein defective in familial HDL deficiency (Tangier disease), which is characterized on the molecular level by the failure of apoA-I to mobilize cholesterol from intracellular stores, to induce cholesterol and phospholipid efflux from cells, and ultimately to initiate the maturation of HDL particles and the HDL-mediated reversed cholesterol transport (Bodzioch et al. 1999; Brooks-Wilson et al. 1999; Rust et al. 1999). Early models explaining ABCA1-mediated lipid efflux from cells assumed that this transporter facilitates translocation of cholesterol and phospholipids to the exofacial leaflet of the cell membrane, where they became accessible for the passive transfer to apoA-I. Further studies, however, provided several pieces of evidence suggesting that apoA-I may directly interact with ABCA1 for the effective unloading of cell cholesterol. For instance, cells obtained from patients with Tangier disease displayed reduced number of apoA-I binding sites, whereas increased apoA-I binding to the cell surface could be observed in cells overexpressing full-length cDNA of ABCA1 (Francis et al. 1995; Wang et al. 2000). Moreover, studies utilizing chemical cross-linking indicated that

apoA-I and ABCA1 are in a very close proximity (<7 Å) characteristic of ligand-receptor interaction, while naturally occurring mutations in extracellular ABCA1 loops profoundly impaired the cross-linking efficiency (Wang et al. 2000; Fitzgerald et al. 2002, 2004; Chroni et al. 2004). The binding of apoA-I to ABCA1 was subsequently found to increase the cell content of ABCA1 protein but not the ABCA1 mRNA abundance suggesting that apoA-I-ABCA1 interaction might be critical to ABCA1 stabilization (Wang et al. 2003). Actually, apoA-I was found to promote both the dephosphorylation of the proline-, glutamic acid-, serine-, and threonine-rich (PEST) sequence in the cytoplasmatic domain of ABCA1 and the recruitment of calmodulin to the specific 1-5-8-14 binding motif localized in a close vicinity to the PEST sequence (Wang et al. 2003; Martinez et al. 2003a; Iwamoto et al. 2010). In this manner, apoA-I binding appears to protect ABCA1 against calpain-mediated proteolysis. In addition, lipid-free apoA-I was found to retard ABCA1 degradation mediated by thiol proteases and thereby to facilitate ABCA1 accumulation on the cell surface (Arakawa and Yokoyama 2002).

The recognition of the apoA-I-ABCA1 complex formation and its stabilization as a mechanism protecting against protease-mediated degradation gave rise to the hypothesis that the interaction of apoA-I with ABCA1 may trigger intracellular signaling cascades that modulate ABCA1 levels and/or ABCA1-mediated lipid transport activity in a posttranslational manner (see Fig. 1 for schematic presentation of ABCA1-induced signaling). Early studies documented that apoA-I enhances phosphatidylcholine (PC) turnover in a specific process mediated by a G-protein-dependent activation of PC-specific phospholipases C and D (PC-PLC and PC-PLD) (Walter et al. 1995, 1996). Later investigations attributed the apoA-I-mediated activation of PC-PLC rather to ABCA1-dependent efflux of sphingomyelin (SPM) and the unspecific depletion of plasma membrane SPM content (Yamauchi et al. 2003). In both cases, stimulation of PC-PLC liberates diacylglycerol (DAG), which is the primary physiological activator of PKC. The activation of both PC-specific phospholipases and PKC seems to be critical for ABCA1-mediated lipid transport. Actually, pharmacological interference with PC-PLC and PC-PLD activation reduced apoA-I-induced cholesterol efflux, whereas exogenous application of their products DAG or phosphatidic acid (PA) partially corrected the cholesterol efflux defect in cells obtained from patients with Tangier disease (Walter et al. 1996; Haidar et al. 2001). Similarly, PKC inhibitors and activators were found, respectively, to block or to enhance apoA-I-induced cholesterol efflux from various cell types including macrophages, smooth muscle cells, and fibroblasts (Mendez et al. 1991; Li and Yokoyama 1995; Li et al. 1997). More recently, it has been suggested that PKC specifically controls the translocation of cholesterol from acylCoA:cholesterol acyltransferase (ACAT)-accessible pools to the as yet poorly defined intracellular cholesterol compartment, where it is available for the ABCA1-mediated release (Yamauchi et al. 2004). In addition, PKC isoform alpha (PKCα) was found to increase ABCA1 phosphorylation at as yet unknown serine sites and thereby to enhance it protection against calpain-mediated proteolysis (Yamauchi et al. 2003). Apelin, a bioactive peptide modulating vascular tone and blood pressure and displaying strong antiatherogenic
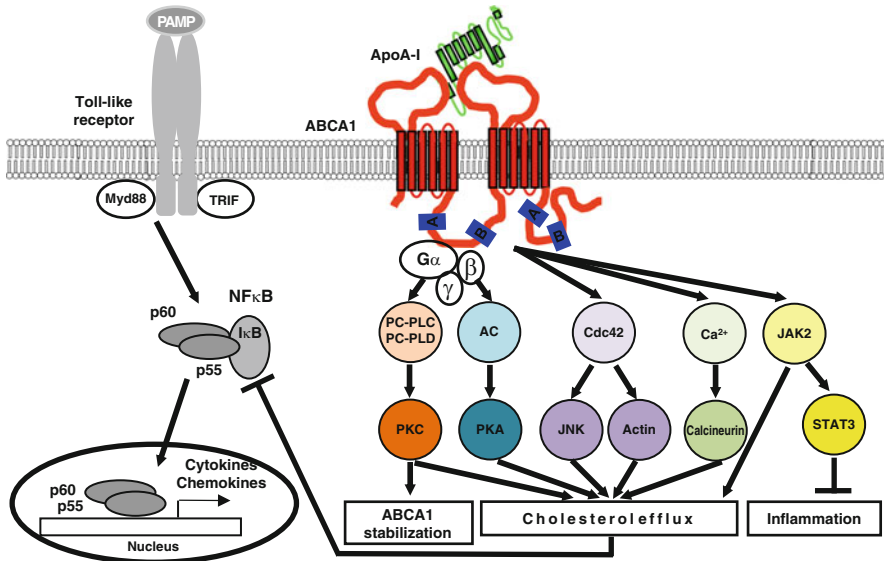
Fig. 1 ApoA-I-induced cell signaling mediated by ABCA1. The binding of apolipoprotein A-I (apoA-I) to lipid transporter ABCA1 induces the trimeric G-protein-mediated activation of phosphatidylcholine-specific phospholipases C and/or D (PC-PLC, PC-PLD) and adenylate cyclase (AC) and the ensuing activation of protein kinases C and A (PKC, PKA). Direct interaction of the small G-protein Cdc42 with ABCA1 induces activation of protein kinase JNK and actin polymerization. Direct interaction of Janus kinase-2 (JAK2) with ABCA1 leads to its autophosphorylation and activation as well as activation of transcription factor signal transducer and activator of transcription 3 (STAT3). These effects account for cholesterol efflux-inducing, anti-inflammatory, and ABCA1-stabilizing properties of apoA-I. In addition, ABCA1-mediated cholesterol efflux to apoA-I exerts indirect negative effect on signal transduction mediated by proinflammatory Toll-like receptors and the resulting activation of the transcription factor NF-κB and expression of cyto- and chemokines. *PAMP* Pathogen-associated molecular patterns

properties, has been recently found to phosphorylate serine residues in ABCA1 through the PKCα pathway and to inhibit calpain-mediated proteolysis, thereby promoting cholesterol efflux and reducing foam cell formation (Liu et al. 2013a).

ABCA1 is well known to be regulated by cyclic adenosine monophosphate (cAMP) at the transcriptional level, and cAMP responsive elements have been localized in the ABCA1 promoter. The interaction of apoA-I with ABCA1, in turn, was demonstrated to activate adenylate cyclase and to increase cAMP content, while severely reduced apoA-I-induced cAMP production was found in cells obtained from carriers of ABCA1 mutations (Haidar et al. 2004). These observations strongly suggested that cAMP and its downstream target protein kinase A (PKA) may represent an important component of apoA-I/ABCA1-induced signaling cascade regulating intracellular lipid translocation and/or their removal from cells. Actually, PKA phosphorylation sites were identified in the nucleotide binding domains of ABCA1, and the targeted mutation of one of these sites, S2054, significantly impaired apoA-I-mediated lipid efflux (See et al. 2002). Moreover,

pharmacological modulation of cAMP/PKA signaling pathway exerted profound effects on apoA-I-induced cholesterol efflux. For instance, forskolin, an adenyl cyclase activator, and 8-Br-cAMP, a stable cAMP analog, substantially increased both ABCA1 phosphorylation and cholesterol efflux to apoA-I in wild-type cells and partly corrected the impaired efflux in cells obtained from patients with Tangier disease (Haidar et al. 2002). Similar effects were more recently observed in macrophages treated with Ht31, a PKA-anchoring inhibitor, which robustly elevated PKA activity in the cytoplasm, elevated ABCA1-dependent cholesterol export from cells, and completely reversed foam cell formation (Ma et al. 2011). Conversely, interference with cAMP/PKA signaling accomplished by treating cells with adenyl cyclase inhibitors, PKA inhibitors, or eicosapentaenoic acid, which decreased both cAMP levels and PKA activity, led to concomitant reduction of ABCA1 phosphorylation and ABCA1-mediated cholesterol efflux (Haidar et al. 2002, 2004; Hu et al. 2009). The molecular mechanisms underlying the stimulatory effect of PKA-mediated ABCA1 phosphorylation on the function of this transporter remain unclear. In contrast to PKC, PKA neither improves ABCA1 stability nor increases apoA-I binding. It seems more likely that phosphorylation of ABCA1 by the cAMP/PKA pathway allows the transporter to assume the conformation favoring more effective lipid translocation across the cell membrane (See et al. 2002).

Janus kinase 2 (JAK2) represents the third kinase, the activity of which is induced by ApoA-I/ABCA1 interaction. Even short exposure of cells expressing ABCA1 to apoA-I produces substantial autophosphorylation of JAK2, which is a prerequisite for further signal transmission to downstream located targets (Tang et al. 2004). Active JAK2 does not seem to directly phosphorylate ABCA1, and it is more likely that it targets an as yet unknown ABCA1 partner protein. Nevertheless, several experimental approaches clearly documented that JAK2 signaling is required for ABCA1 to effectively mediate lipid export from cells. For instance, JAK2-specific inhibitors substantially reduced apoA-I-induced cholesterol efflux, and mutant cells lacking JAK2 exhibited a severely impaired lipid transport (Tang et al. 2004, 2006). In addition, studies exploiting various ABCA1 variants revealed close interdependency between lipid export and JAK2 activation (Vaughan et al. 2009). In contrast to PKC and PKA, JAK2 activation by apoA-I neither promotes ABCA1 stability nor enhances intrinsic lipid translocase activity of the transporter. However, JAK2 activation seems to be critical for the optimum formation of apoA-I/ABCA1 complex, as JAK2-deficient cells exhibit severely impaired apoA-I binding despite normal ABCA1 protein levels (Tang et al. 2006).

JAK2 autophosphorylation is commonly followed by phosphorylation of several downstream targets, out of which signal transducer and activator of transcription 3 (STAT3) represents its canonical target. As ABCA1 possesses STAT3 docking sites, this molecule was an obvious candidate for linking JAK2 with ABCA1 activation. As a matter of fact, apoA-I induces STAT3 phosphorylation (which is tantamount to its activation) in an ABCA1-dependent fashion, and this effect is attenuated in cells expressing ABCA1, in which STAT3 docking sites have been mutated (Tang et al. 2009). However, neither complete STAT3 deficiency nor

interruption of ABCA1-STAT3 interaction altered ABCA1 capacity to bind apoA-I and to efflux cholesterol from cells (Tang et al. 2009). Hence, apoA-I-induced STAT3 activation seems dispensable for the ABCA1-mediated lipid export. STAT3 represents an intracellular target of IL-10—a cytokine with well-established anti-inflammatory properties—and activation of STAT3 was demonstrated to suppress several aspects of inflammatory macrophage activation. These observations raised the interesting possibility that apoA-I might produce anti-inflammatory effects by activating STAT3 in ABCA1-dependent fashion. Actually, exposure of ABCA1-expressing macrophages to apoA-I suppressed lipopolysaccharide (LPS)-induced production of proinflammatory cytokines such as interleukin-6 (IL-6), and this effects were abolished after pharmacological STAT3 blockade or knocking down STAT3 expression with siRNA (Tang et al. 2009). Further investigations demonstrated that the suppressing effect of apoA-I on LPS-induced cytokine production was mediated by mRNA destabilization brought about by mRNA-destabilizing protein tristetraprolin, the expression of which was induced in cells exposed to apoA-I in an ABCA1- and JAK2/STAT3-dependent manner (Yin et al. 2011). Recently, apoA-I was demonstrated to promote cyclooxygenase-2 (COX-2) activation and prostacyclin (PGI$_2$) production in endothelial cells, and these anti-inflammatory effects were also found to depend on ABCA1 and JAK2 activation (Liu et al. 2011).

Cell division control protein 42 (Cdc42) is a member of a small G-protein family involved in the regulation of cytoskeleton organization and intracellular vesicular trafficking. Early studies revealed decreased Cdc42 expression and abnormal cytoskeleton architecture in cells obtained from Tangier patients (Hirano et al. 2000). Moreover, impaired cholesterol efflux observed in aged human fibroblasts as well as fibroblasts from Werner syndrome characterized by the early onset of senescent phenotypes including premature atherosclerotic cardiovascular disease could be corrected by forced expression of wild-type Cdc42 (Tsukamoto et al. 2002; Zhang et al. 2005). Expression of constitutively active Cdc42 variant in normal Madin-Darby canine kidney (MDCK) cells potentiated apoA-I-induced cholesterol efflux, whereas expression of dominant negative Cdc42 variants in normal MDCK cells or fibroblasts exerted opposite effects (Hirano et al. 2000; Nofer et al. 2003). ApoA-I-induced cholesterol efflux was also reduced in cells pretreated with *Clostridium difficile* toxin, which irreversibly modifies and disables Cdc42 (Nofer et al. 2003). Both Cdc42 and ABCA1 were found to co-segregate into lubrol-insoluble, triton-soluble lipid rafts (Drobnik et al. 2002). In addition, Cdc42 could be immunoprecipitated with wild-type ABCA1, but not with C-terminally truncated variant of this transporter indicating that both proteins interact with each other and suggesting that C-terminus of ABCA1 harbors a potential docking site for Cdc42 (Tsukamoto et al. 2001; Nofer et al. 2006). Exposure of cells expressing wild-type ABCA, but not cells obtained from Tangier patients or expressing C-terminally truncated variant of ABCA1 to apoA-I, induced Cdc42 activation and subsequent actin polymerization (Nofer et al. 2006). Taken together, these findings suggest that apoA-I signals through ABCA1 to activate Cdc42 and thereby to promote cholesterol efflux. How exactly Cdc42 activation promotes lipid export from cells remains

to be elucidated. One possibility is that Cdc42 modulates intracellular vesicular traffic and thereby helps to supply cholesterol and/or phospholipids to an intracellular compartment, where they are available for the ABCA1-mediated release. The retardation of intracellular lipid transport in cells with reduced Cdc42 levels and its intensification after enforced expression of Cdc42 appears to support this concept (Tsukamoto et al. 2002). Alternatively, components of the signaling machinery localized downstream to Cdc42 might accelerate intracellular lipid transfer or the ABCA1-dependent lipid translocation across the cell membrane. Actually, apoA-I was demonstrated to produce consecutive activation of two serine/threonine kinases, namely, p21-activated kinase 1 (PAK1) and c-Jun N-terminal kinase (JNK) in ABCA1- and Cdc42-dependent manner (Nofer et al. 2003). The potential involvement of these two kinases in the processes of lipid export from cells has been not clarified to date.

Mobilization of intracellular Ca(2+) from intracellular stores or Ca(2+) influx from extracellular space represents an integral component of diverse intracellular signaling pathways. In one single report, evidence has been provided that apoA-I provokes extracellular Ca(2+) influx in an ABCA1-dependent manner and that inhibition of calcineurin, the downstream target of Ca(2+) influx, with cyclosporine A or FK506 completely abolished apoA-I lipidation and also interfered with JAK2 phosphorylation (Karwatsky et al. 2010). However, other authors failed to observe Ca(2+) mobilization in fibroblasts or smooth muscle cells after exposure to apoA-I or other apolipoproteins (apoA-II, apoC-III) (Nofer et al. 2000 and unpublished observations). Further studies are necessary, therefore, to fully understand the contribution of Ca(2+) mobilization to ABCA1-mediated signaling and lipid export.

3 ApoA-I-Induced Cell Signaling Indirectly Mediated by β-ATPase and P2Y$_{12/13}$ ADP Receptor

F1F0 ATP synthase is the terminal enzyme of the oxidative phosphorylation pathway responsible for the lion part of ATP synthesis in humans and other living being except in Archaea and present in mitochondria, chloroplasts, and prokaryotic membranes. Unexpectedly, the F1F0 ATP synthase (with F1 domain facing outside) has been found on the surface of several cells including hepatocytes, adipocytes, and endothelial cells, and its β-chain (β-ATPase) has been characterized as a receptor for apoA-I (Martinez et al. 2003b; Fabre et al. 2006; Radojkovic et al. 2009; Howard et al. 2011). The binding of apoA-I to β-ATPase induces ATP hydrolysis and promotes extracellular ADP generation, which in turn stimulates intracellular signaling by activating purinergic receptors, which belong to the family of G-protein-coupled receptors stimulated by extracellular nucleotides (Martinez et al. 2003b; Fabre et al. 2006). In hepatocytes, the β-ATPase/P2Y$_{13}$-induced signaling was reported to activate the small G-protein RhoA and the downstream-located Rho-associated protein kinase (ROCK-I) and thereby to promote HDL endocytosis by as yet poorly defined mechanism (Fabre et al. 2006;

Malaval et al. 2009). In endothelial cells, binding of apoA-I to β-ATPase and the subsequent generation of extracellular ADP stimulated endothelial proliferation and survival, but components of intracellular signaling cascade responsible for these effects remained uncharacterized (Radojkovic et al. 2009). In a recent study, the activation of β-ATPase/$P2Y_{12}$ was found to precede HDL binding and cell association as well as ABCG1- and SR-BI-dependent internalization, and transcytosis in endothelial cells (Cavelier et al. 2012). The identity of intracellular signaling pathway linking $P2Y_{12}$ activation to HDL internalization has not been addressed in this study.

4   ApoA-I- and HDL-Induced Cell Signaling Indirectly Mediated by ABCA1 and/or ABCG1

ABCA1 is unique among ABC transporters in that it requires the direct binding of acceptors for the transported substances. ATP-binding cassette transporter G1 (ABCG1) was also found to be a crucial mediator of lipid export. Studies by Wang et al. demonstrated that ABCG1 promotes efflux to a variety of acceptors, including HDL, low-density lipoprotein (LDL), phospholipid vesicles, and cyclo-dextrin (Wang et al. 2004, 2006). In major contrast to ABCA1, ABCG1 does not engage into direct interaction with lipid acceptors and for this reason cannot serve as a triggering element of intracellular second messenger cascade. However, recent studies document that ABCG1 (and to lesser extent ABCA1) profoundly impacts on signaling processes taking place in contiguity. Several studies showed that ABCA1 regulates cholesterol distribution between raft and non-raft membrane fractions and pointed to increased lipid raft formation in macrophages and other cells deficient in ABCG1 and ABCA1 (Landry et al. 2006; Sano et al. 2007; Koseki et al. 2007; Zhu et al. 2008a, Yvan-Charvet et al. 2008). Lipid rafts provide a molecular platform securing efficient signal transduction through several receptor families including proinflammatory Toll-like receptors (TLRs). Not surprisingly, therefore, both ABCA1-deficient cells and ABCG1-deficient cells, and in particular cells lacking both ABC transporters, exhibited increased cell surface expression of TLR4 and sensitivity to LPS stimulation (Koseki et al. 2007; Zhu et al. 2008a, Yvan-Charvet et al. 2008; Mogilenko et al. 2012). Also the NF-κB activation-dependent cytokine and chemokine release in response to stimulation with agonists of other TLR receptors (TLR2, TLR3) or other proinflammatory receptors (CD40) revealed to be increased in macrophages deficient in ABCA1 and/or ABCG1 (Sun et al. 2009; Yin et al. 2012). Such cells were also found to be prone to apoptosis during efferocytosis (phagocytosis of apoptotic cells) as compared to wild-type cells (Yvan-Charvet et al. 2010a). The enhanced apoptotic response observed in ABCA1- and ABCG1-deficient macrophages was dependent on an excessive assembly of NADPH oxidase/NOX2 complexes within lipid rafts followed by oxidative burst and ensuing sustained JNK activation, which turned on the apopto-tic cell death program. It is very likely that similar mechanisms consisting in amplification of transmembrane signaling under conditions of decreased ABCG1

and/or ABCA1 activity and the resulting accumulation of lipid rafts may substantially contribute to the enhancement of several proinflammatory processes. For instance, cholesterol accumulation within lipid rafts was suggested to enhance monocyte adhesion and neutrophil activation, and both processes could be reversed by cholesterol removal from cells carried out either with help of synthetic cholesterol acceptors (e.g., cyclodextrin) or through induction of ABCA1-dependent cholesterol efflux (Murphy et al. 2008, 2011). In addition, ABCG1- and ABCA1-dependent modulation of cell membrane cholesterol content was demonstrated to critically regulate cellular signaling related to proliferatory responses. For instance, mice deficient in ABCG1- and ABCA1 developed severe monocytosis and neutrophilia, which was dependent on uncontrolled proliferation and expansion of hematopoietic stem progenitor cells (HSPC) (Yvan-Charvet et al. 2010b). The mechanistic analysis revealed increased plasma membrane lipid raft formation in these cells accompanied by elevated cell surface presence of interleukin IL-3/ granulocyte macrophage colony-stimulating factor (GM-CSF) receptor. Addition of IL-3 or GM-CSF to ABCA1/G1-deficient bone marrow led to increased proliferation of HSPCs, reflecting activation of signaling pathways downstream of the IL-3/GM-CSF receptor. Similarly, defects in cholesterol efflux pathways in macrophages and dendritic cells in spleens of ABCA1/G1-deficient mice led to increased production of IL-23 and activation of a proinflammatory and proatherogenic signaling axis involving IL-23/IL-17 (Westerterp et al. 2012). Other studies showed increased lipid raft content in plasma membrane and enhanced proliferation in response to anti-CD3 antibody stimulation in T cells obtained from ABCG1-deficient animals (Bensinger et al. 2008). Similar increase in lymph node T-cell proliferation has been noted after disruption of cholesterol efflux pathway by deletion of apoA-I on a hypercholesterolemic background (Wilhelm et al. 2009).

5   HDL-Induced Cell Signaling Mediated by SR-BI

Scavenger receptor type I (SR-BI) is a cell surface glycoprotein originally identified by its homology to the scavenger receptor CD36 and capacity to bind acetylated LDL. Later studies in vitro revealed that SR-BI serves as the binding partner for a variety of ligands including native and oxidized LDL, very-low-density lipoproteins (VLDL), Lp(a), modified serum proteins such as maleylated albumin, lipid vesicles containing negatively charged phospholipids, apoptotic cells, and HDL. Despite this promiscuous binding behavior SR-BI is believed to primarily function as a physiologically relevant HDL receptor because of its tissue expression pattern reflecting sites of HDL cholesterol uptake and because of the profound impact of complete or tissue-specific SR-BI deficiency on HDL metabolism. The classic cellular function of SR-BI is to mediate the selective uptake of lipids from HDL and to transfer them into cells. Cholesteryl esters represent the primary substrate for SR-BI, but this receptor also facilitates transfer of various other lipid species including unesterified cholesterol, phospholipids, triglycerides, and lipid-

soluble vitamins. SR-BI also mediates the efflux of cholesterol from cells to HDL, which in contrast to ABCA1- and ABCG1-mediated efflux is a passive, concentration gradient-dependent, and energy-independent process. Importantly, SR-BI-mediated lipid transfer from and to HDL occurs in the absence of consecutive internalization and degradation of HDL particle, which is a precedent condition for effective signal transduction (for recent reviews, see Hoekstra et al. 2010; Mineo and Shaul 2012).

Binding of HDL to SR-BI has been demonstrated to trigger several intracellular signaling events (see Fig. 2). The recruitment of non-receptor tyrosine kinase src to the C-terminal cytoplasmic tail of SR-BI followed by src autophosphorylation and phosphorylation and activation of AMP-activated protein kinase (AMPK) mediated through calcium/calmodulin-dependent protein kinase (CAMK) and/or serine/threonine liver kinase B1 (LKB1) appear to constitute initial steps in SR-BI signaling
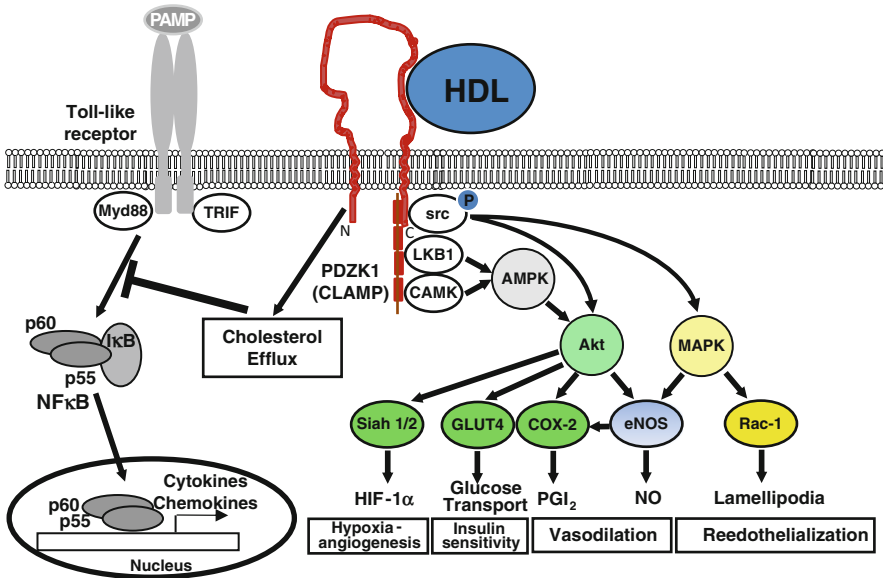

Fig. 2 HDL-induced cell signaling mediated by SR-BI. The binding of HDL to scavenger receptor type 1 (SR-BI) induces activation of protein kinases src, liver kinase B1 (LKB1), and calcium calmodulin-dependent protein kinase (CAMK) in a process dependent on an adapter protein PDZK1 (CLAMP). The resulting activation of AMP-activated protein kinase (AMPK) and protein kinase Akt as well as mitogen-activated protein kinase (MAPK) transduces signal to downstream effectors including endothelial nitric oxide synthase (eNOS) generating NO, cyclooxygenase-2 (COX-2) producing prostacyclin (PGI_2), glucose transporter GLUT4 mediating cellular glucose uptake, ubiquitin ligases Siah 1 and 2 stabilizing hypoxia-inducible factor-1α (HIF-1α), and small G-protein Rac-1 regulating formation of lamellipodia. These effects account for vasodilatory, insulin-sensitizing, proangiogenic, and endothelial regenerating properties of HDL. In addition, SR-BI-mediated cholesterol efflux to HDL exerts indirect negative effects on signal transduction mediated by proinflammatory Toll-like receptors and the resulting activation of the transcription factor NF-κB and expression of cyto- and chemokines. Pathogen-associated molecular patterns (PAMP)

(Mineo et al. 2003; Kimura et al. 2010). Detailed studies revealed that phosphorylations of src (though not its interaction with SR-BI) and AMPK are critically dependent on the presence of the PDZ domain-containing adaptor protein, PDZK1 (also termed CLAMP), which interacts with extreme C-terminal residues of SR-BI and is essential for its stability in the plasma membrane (Kimura et al. 2010; Assanasen et al. 2005; Zhu et al. 2008a, b). Src and AMPK activations lead to the activation of phosphatidylinositol 3-kinase (PI3K), which in turn induces parallel activation of protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) (Kimura et al. 2010; Assanasen et al. 2005; Zhu et al. 2008b). The latter event seems to be required for the subsequent stimulation of the activity of small G-protein Rac1, which promotes formation of lamellipodia and induces cell shape change (Seetharam et al. 2006). It remains currently unclear, whether SR-BI-mediated lipid transfer is required for the effective initiation of signaling by HDL. The C-terminal transmembrane domain of SR-BI contains a cholesterol-binding site, which interacts with plasma cholesterol, as could be documented in photocholesterol binding experiments (Assanasen et al. 2005). Studies utilizing SR-BI/CD36 chimeras showed that only transfer of both C-terminal domains (cytoplasmatic and transmembrane) endows CD36 with signaling properties of SR-BI, whereas the transfer of the C-terminal cytoplasmatic domain only is insufficient (Assanasen et al. 2005). In addition, introduction of mutations into the transmembrane C-terminal domain severely impeded SR-BI-mediated signal transduction (Saddar et al. 2013). Other studies pointed to the enhancement of SR-BI signaling in the presence of extracellular cholesterol acceptors such as cyclodextrins or reconstituted HDL particles containing 2 molecules of apoA-I but not cholesterol (Assanasen et al. 2005). Furthermore, HDL enriched in phosphatidylcholine, which increases its cholesterol acceptor capacity, induces signal transduction at concentrations that are otherwise insufficient to invoke signaling. Collectively, these observations suggest that SR-BI-mediated cholesterol efflux exerts at least potentiating effects on HDL-triggered signaling transduced by this receptor. Recently, Al-Jarallah and Trigatti hypothesized that SR-BI-mediated removal of cholesterol from caveolae might suppress the activity of high molecular weight phosphatase complex, which would in turn help to maintain protein kinase targets such as MAPK in the phosphorylated state and to prolong their activation (Al-Jarallah and Trigatti 2010). Whether this mechanism indeed contributes to HDL-induced signaling mediated by SR-BI remains to be clarified.

The concerted activation of both Akt and MAPK appears to constitute the centerpiece of SR-BI-triggered signaling cascades. Both kinases are required for phosphorylation and full activation of endothelial nitric oxide synthase (eNOS), nitric oxide generation, and vasorelaxation, which are observed in endothelial cells or isolated aortas in the presence of HDL (Yuhanna et al. 2001; Mineo et al. 2003; Assanasen et al. 2005). In addition, PI3K/Akt/eNOS signaling was found to be involved in the HDL-induced COX-2 expression and PGI_2 release in endothelial cells (Zhang et al. 2012). The proliferation of bone-derived mesenchymal stem cells in response to HDL was likewise mediated via its binding to scavenger receptor-B type I and activation of PI3K/Akt/MAPK pathways (Xu et al. 2012). Activation of

MAPK but not Akt with subsequent induction of Rac1-GTPase was demonstrated to promote HDL-induced endothelial cell migration, which is critical for carotid artery reendothelialization after perivascular electric injury (Seetharam et al. 2006). Conversely, activation of Akt but not MAPK was necessary to sustain the migration and the proliferation of breast cancer cells (Danilo et al. 2013). In adipocytes, SR-BI-mediated activations of Akt and AMPK were found to promote glucose uptake and translocation of the glucose transporter GLUT4 to the plasma membrane suggesting that SR-BI signaling might contribute to insulin-sensitizing effects of HDL (Zhang et al. 2011). Finally, augmentation of hypoxia-induced angiogenesis, which is observed in the presence of HDL, was demonstrated to depend on SR-BI-mediated activation of Akt linked to increased expression of E3 ubiquitin ligases Siah1 and Siah2 and accelerated degradation of prolyl hydroxylases (PHD1-PHD3) combined with stabilization of hypoxia-inducible factor 1α (HIF-1α) (Tan et al. 2013). Recent studies provide evidence that similar to ABCG1 also SR-BI may indirectly affect proinflammatory signaling by reducing membrane cholesterol content. Actually, macrophages obtained from SR-BI-deficient animals were characterized by increased inflammatory responses to Toll-like receptor agonists (Guo et al. 2009; Cai et al. 2012). Feng et al. found that SR-BI deficiency enhanced lymphocyte proliferation, caused imbalanced interferon-γ (IFNγ) and IL-4 production in lymphocytes, and led to elevated inflammatory cytokine production in macrophages (Feng et al. 2011). Umemoto et al. demonstrated that HDL-induced disruption of lipid raft in adipocytes, which is accompanied by reduced activation of NADPH oxidase and production of monocyte chemotactic protein 1 (MCP1), was reversed by silencing both ABCG1 and SR-BI expression (Umemoto et al. 2013).

It is well established that HDL inhibits the activation of platelets by strong agonists such as thrombin and collagen (for review, see Nofer and van Eck 2011). The presence of SR-BI has been identified on platelet surface (Imachi et al. 2003). Recent investigations demonstrated that HDL binding to platelets was reduced in a concentration-dependent fashion by SR-BI ligands such as negatively charged liposomes, which in addition potently inhibited thrombin-induced platelet aggregation, granule secretion, fibrinogen binding, and mobilization of intracellular Ca^{2+} (Nofer et al. 2011). Furthermore, both native HDL and other SR-BI ligands failed to inhibit thrombin-induced activation of platelets obtained from SR-BI-deficient mice. These findings together with the results of Imachi et al. (2003), who observed an inverse relationship between the levels of SR-BI expression and the platelet aggregation in response to ADP, corroborate the hypothesis that SR-BI is a true functional HDL receptor on platelets. The likely consequence of the HDL binding to SR-BI on platelets is the induction of intracellular second messenger cascade. It has been previously demonstrated that incubation of platelets with HDL leads to the release of DAG from the plasma membrane phosphatidylcholine and to subsequent activation of PKC, which in turn stimulates the Na^+/H^+ antiport, promotes the alkalization of the cytoplasmic compartment, and inhibits the release of calcium ions from intracellular storage sites (Nofer et al. 1996). In addition, activation of PKC inhibits the activity of phosphatidylinositol-specific phospholipase C (PI-PLC), which is one of

the most important signal transduction mediators of agonists such as thrombin and collagen (Nofer et al. 1998). It is conceivable that this signaling cascade is launched by interaction of HDL with SR-BI on platelet surface.

6 HDL-Induced Cell Signaling Mediated by S1P

Early studies on HDL-induced signal transduction focused on apoA-I or other apolipoproteins as potential binding partners for HDL receptor responsible for initiating the cascade of intracellular signaling events. However, it has soon become clear that neither apoA-I nor other proteins encountered in HDL particles can exclusively account for HDL signaling activities. Studies utilizing fibroblasts demonstrated that PI-PLC activation, which is observed in cells exposed to HDL and accompanied by increased phosphatidylinositol bisphosphate (PIP_2) turnover and the mobilization of intracellular calcium, is not emulated by purified apoA-I or apoA-I-containing proteoliposomes, but occurs in the presence of lipids extracted from HDL holoparticles (Nofer et al. 2000). Likewise, certain cellular responses triggered by HDL in fibroblasts of smooth muscle cells such as cell proliferation or proliferation-linked activation of MAPK could be observed in the presence of HDL lipids or HDL particles, in which proteins were covalently modified or enzymatically degraded, but not in the presence of proteins isolated from HDL (Deeg et al. 1997; Sachinidis et al. 1999; Nofer et al. 2001a). The intense search for lipid species accounting for the signal-inducing capacity of HDL revealed that these lipoproteins serve as a carrier for bioactive lysosphingolipids such as sphingosine-1-phosphate (S1P), sphingosylphosphorylcholine (SPC), and lysosulfatide (LSF) and that signaling events observed in cells exposed to native HDL or isolated lysosphingolipids largely overlap (Sachinidis et al. 1999; Nofer et al. 2000, 2004; Kimura et al. 2001).

S1P is the most prominent and best characterized member of the lysosphingolipid family. It is produced by phosphorylation of sphingosine by sphingosine kinases 1 and 2 (SK1 and SK2) in response to a variety of stimuli and degraded to phosphoethanolamine and hexadecanal by S1P-lyase or to sphingosine and organic phosphate by S1P phosphatase. S1P interacts with five related G-protein-coupled receptors termed $S1P_{1-5}$, which regulate a wide spectrum of cellular functions, including proliferation and survival, cytoskeletal rearrangements, and cell motility, and exert potent cytoprotective effects. In the vasculature, S1P receptors were identified on endothelial and smooth muscle cells, and S1P provides essential contribution to the new vessel formation and the maintenance of vascular barrier integrity. In addition, S1P was demonstrated to interfere with proliferation, migration, and activation of monocytes/macrophages and to regulate their recruitment to sites of inflammation (for recent reviews, see Maceyka et al. 2012; Levkau 2013). Erythrocytes and platelets are major sources of S1P in plasma, where it is preferentially (up to 60 %) associated with HDL subfraction rich in apolipoprotein M (apoM) (Dahm et al. 2006; Hänel et al. 2007; Christoffersen et al. 2011). Recent studies demonstrate that apoM specifically binds S1P and stimulates its biosynthesis for secretion (Liu et al. 2013b). There is substantial evidence suggesting that S1P may

directly contribute to atheroprotective effects attributed to HDL. For instance, S1P closely correlates with HDL in a concentration range, in which HDL most effectively protects against atherosclerosis, and decreased HDL-bound S1P levels were noted in patients with coronary artery disease and myocardial infarction (Karuna et al. 2011; Sattler et al. 2010; Argraves et al. 2011). In addition, S1P was found to emulate in vitro several atheroprotective effects of HDL, which themselves could be attenuated by interrupting signaling through S1P receptors (Levkau et al. 2013).

Protein kinases MAPK, AMPK, and Akt are critical for the S1P-dependent signaling cascade, which unfolds in endothelial cells in the presence of HDL (see Fig. 3 for schematic presentation of S1P-mediated signaling). Kimura and
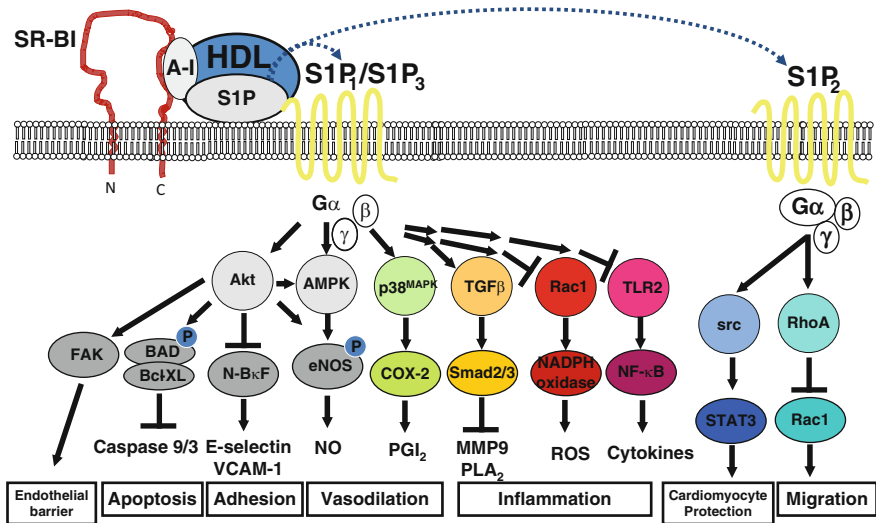

Fig. 3 HDL-induced cell signaling mediated by S1P. The binding of HDL to scavenger receptor type I (SR-BI) may provide a molecular platform for efficient receptor stimulation by sphingosine-1-phosphate (S1P) present in HDL molecule. Activation of AMP-activated protein kinase (AMPK) and protein kinase Akt via $S1P_1$ and/or $S1P_3$ receptors leads to the stimulation of focal adhesion kinase (FAK), the inactivation of proapoptotic protein BAD and the inhibition of caspases 9 and 3, the inhibition of the transcription factor NF-κB and the expression of adhesive molecules E-selectin and vascular cell adhesion molecule 1 (VCAM-1), as well as the activation of endothelial nitric oxide synthase (eNOS) and the generation of NO. Activation of the mitogen-activated protein kinase p38MAPK results in activation of cyclooxygenase-2 (COX-2) and production of prostacyclin (PGI_2). Increased expression of transforming growth factor β (TGFβ) contributes to the increased activation of transcription factors Smad 2 and 3, which suppress production of proinflammatory matrix metalloproteinases such as MMP9 as well as phospholipase A_2 (PLA_2). Inhibition of small G-protein Rac1 suppresses activity of NADPH oxidase and generation of reactive oxygen species. Inhibition of Toll-like receptor 2 (TLR2) reduces NF-κB activation and production of proinflammatory cytokines. These effects account for endothelial barrier-enhancing, anti-inflammatory, antiapoptotic, anti-adhesive, and vasodilatory properties of HDL. Activation of protein kinase src and transcription factor signal transducer and activator of transcription 3 (STAT3) via $S1P_2$ protects against cardiomyocyte apoptosis. Activation of the small G-protein RhoA via $S1P_2$ leads to inhibition of the small G-protein Rac1, which regulates smooth muscle cell migration

colleagues demonstrated that activation of MAPK is essential for endothelial proliferation and survival mediated by HDL-associated lysosphingolipids (Kimura et al. 2001). Using antisense oligonucleotides and siRNA strategy combined with application of pharmacological G-protein inhibitors, they further show that S1P receptor types 1 and 3 and inhibitory G-protein (Gi) contribute to HDL-mediated induction of endothelial migration, whereas the augmentation of endothelial survival in endothelial cells exposed to HDL is exclusively dependent on S1P$_1$. Miura et al. demonstrated that HDL promotes endothelial cell tube formation via activation of MAPK and suggested that this effect is mediated by S1P present in HDL particles (Miura et al. 2003). Later these authors showed that reconstituted HDL particles enriched in S1P are particularly effective in stimulating angiogenic response (Matsuo et al. 2007). HDL-like lipoproteins are also present in follicular fluid and induce angiogenesis in the S1P- and MAPK-dependent manner (von Otte et al. 2006). The activation of AMPK, which itself was entirely dependent on the parallel activation of CAMK, was localized upstream to Akt in the signaling sequel (Kimura et al. 2010). The stimulation of Akt by HDL-associated lysosphingolipids was—depending on the experimental system used—mediated by either S1P$_1$ or S1P$_3$ and controlled an array of important antiatherogenic activities attributed to HDL. Nofer et al. (2001b) found that activation of Akt by HDL and its associated lysosphingolipids disabled a proapoptotic protein BAD and thereby inhibited the collapse of mitochondrial potential, the cytochrome C release from mitochondria, and the ensuing activation of apoptosis-executing caspases 3 and 9. Nofer et al. (2004) and Kimura et al. (2006) demonstrated that the S1P content in HDL at least partially accounts for the HDL-stimulated activation of eNOS, generation of NO, and vasorelaxation. Stimulation of endothelial cells with statins such as pitavastatin or simvaststin increased the expression of S1P$_1$ and potentiated the stimulatory effect of HDL on eNOS activation (Igarashi et al. 2007; Kimura et al. 2008). Likewise, upregulated S1P$_1$ and S1P$_3$ expression and increased Akt and eNOS activation were found in fenofibrate-treated mice, which were characterized by elevated plasma levels of HDL and S1P (Krishna et al. 2012). Kimura et al. (2006) reported that signaling through S1P$_1$ receptor partly accounts for the inhibitory effects exerted by HDL on tumor necrosis factor α (TNFα)-induced NF-κB activation as well as endothelial expression of adhesins such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Argraves et al. (2008) found that HDL increased endothelial barrier integrity as measured by electric cell substrate impedance sensing in a process that was entirely dependent on S1P, S1P$_1$ expression, and Akt activation. The favorable effect of S1P on endothelial barrier was sustained for considerably longer time with HDL-associated rather than albumin-associated S1P, and this was related to the inhibitory effect of HDL on S1P$_1$ degradation (Wilkerson et al. 2012). Norata et al. reported that HDL potently stimulates endothelial expression of long pentraxin 3—a key component of innate immunity—as well as transforming growth factor-β (TGFβ), a compound with potent anti-inflammatory and immuno-modulatory activities, in Akt-dependent manner. They attributed these effects to the presence of S1P and SPC in HDL particles and S1P$_1$ and S1P$_3$ receptors on

endothelial cells (Norata et al. 2005, 2008). Increased activation of Smad 2/3, a transcription factor controlled by TGFβ, found in the latter study suggests that HDL-associated S1P may transactivate TGFβ signaling pathways in an autocrine fashion. Most recently, Tatematsu et al. reported that endothelial lipase (EL) is a critical determinant of HDL-stimulated S1P-dependent signaling (Tatematsu et al. 2013). Actually, HDL-induced endothelial cell migration and angiogenic responses as well as Akt activation were markedly decreased in EL-deficient endothelial cells, but restored in the presence of exogenous S1P. Basing on application of pharmacological inhibitors, Tatematsu and colleagues concluded that the effects of HDL on endothelial cell migration and Akt activation are mediated by $S1P_1$.

As pointed out above, HDL is strongly mitogenic for smooth muscle cells, and HDL-associated lysosphingolipids appear to account for this effect. On the other hand, HDL was identified as a potent inhibitor of smooth muscle cell migration, which is a hallmark of the development of advanced atherosclerotic plaque and restenosis (Tamama et al. 2005; Damirin et al. 2007). The inhibitory effect of HDL was likely mediated by its S1P content, as it was abolished in the presence of $S1P_2$-specific siRNA and following desensitization of S1P receptors and much enhanced in cells overexpressing $S1P_2$ receptor. Further effects exerted by HDL on smooth muscle cell through its S1P content include modulation of the activity of several vasoactive factors. Chrisman et al. found that HDL-associated S1P desensitizes guanylyl cyclase B, a receptor for C-type natriuretic peptide (CNP), and thereby inhibits CNP-induced cyclic guanosine monophosphate (cGMP) accumulation in vascular smooth muscle cells (Chrisman et al. 2003). Gonzalez-Diez and colleagues demonstrated induction of COX-2 expression and PGI_2 production in vascular smooth muscle cells exposed to HDL, which was mediated through S1P receptors 2 and 3 and protein kinase p38MAPK (González-Díez et al. 2008). They have also shown that simvastatin potentiates the HDL- and S1P-induced COX-2 expression by upregulating cellular levels of $S1P_3$. Finally, HDL-associated lysosphingolipids S1P and SPC were found to suppress the proinflammatory activation of smooth muscle cells brought about by stimulation with thrombin and characterized by the increased release of inflammatory cyto- and chemokines such as MCP1 (Tölle et al. 2008). The detailed examination of signaling pathways accounting for inhibitory effects exerted by HDL-associated lysosphingolipids revealed that they were related to the inhibition of Rac1-mediated activation of NADPH oxidase and generation of reactive oxygen species. $S1P_3$ was identified to mediate anti-inflammatory effects of HDL, S1P, and SPC in smooth muscle cells.

Cardiomyocytes express several S1P receptors, and HDL was found to exert protective effects on these cells through its S1P content. HDL and S1P showed potent capacity to protect cardiomyocytes against hypoxia-reoxygenation- or doxorubicin-induced apoptosis, and these effects were attributed to the induction of protein kinases Src, MAPK, and Akt and the transcription factor STAT3 (Frias et al. 2009, 2010; Tao et al. 2010). However, investigations concerning the identity of receptor-mediating protective effects of HDL-associated S1P were inconclusive, and equally supportive evidence for the involvement of either $S1P_2$

or $S1P_1$ and $S1P_3$ has been provided. Recently, short-term treatment of cardiomyocytes with HDL or S1P was found to induce a PKC-dependent phosphorylation of connexin43, which is a gap junction protein present in ventricular cardiomyocytes and involved in cardioprotection by modulating ischemic preconditioning (Morel et al. 2012). In addition, HDL and S1P improved gap junctional communication, but only incrementally affected conduction velocities in cardiomyocytes. The physiological relevance of these effects has been clearly documented using an ex vivo approach, in which both HDL and S1P protected perfused hearts against ischemia/reperfusion-induced cell death.

Several other cell types were found to be responsive to stimulation with HDL-associated lysosphingolipids, but the physiological relevance of these effects remains obscure. For instance, HDL and S1P were demonstrated to stimulate prostate cancer cell migration and invasion through S1P receptors 2 and 3 and activation of MAPK and STAT3, to stimulate plasminogen activator inhibitor-1 (PAI-1) release from adipocytes through $S1P_2$ and activation of PKC and Rho kinase, and to promote release of fibroblast growth factor-2 (FGF2), a potent neurotrophic factor, from astroglial cells through activation of PI-PLC and MAPK (Malchinkhuu et al. 2003; Lee et al. 2010; Sekine et al. 2011). HDL particles isolated from body fluids other than plasma were also found to contain S1P and to stimulate intracellular signaling through their S1P content. For instance, HDL-like particles obtained from cerebrospinal fluid stimulated astrocyte migration and oligodendrocyte retraction in a manner sensitive to inhibitors of S1P receptors 1 and 3 (Sato et al. 2007). Follicular fluid-derived HDL was found to promote human granulosa lutein cell migration through $S1P_3$ and activation of small G-protein Rac1 (Becker et al. 2011). Despite the prominent role played by monocytes and macrophages in the pathogenesis of atherosclerosis, very little is known about the modulatory effects exerted by S1P cargo of HDL particles on these cells. In one study, both HDL and S1P were found to blunt monocyte activation induced by agonists of TLR2, but the attribution of this effect to the HDL-associated S1P was not unequivocally demonstrated (Dueñas et al. 2008).

7   HDL-Induced Cell Signaling: Future Challenges and Opportunities

HDL constitutes a large and heterogenous macromolecule carrying more than 50 proteins, several amphipathic peptides, miRNAs, and hundreds of lipid species representing almost all known lipid classes. Several proteins and lipids identified in HDL—among others, apolipoprotein H, haptoglobin, and steroid hormones—are recognized receptor ligands and inductors of intracellular signaling events. However, the rigid evidence demonstrating that these proteins or lipids contribute to the HDL-induced signaling governing diverse functional responses to this lipoprotein has been not provided to date or is at best equivocal. For instance, several studies documented that HDL carries estradiol in the form of fatty acyl esters produced in a reaction catalyzed by LCAT. HDL-derived estradiol esters are internalized via SR-

BI-mediated mechanisms and subsequently hydrolyzed intracellularly to unfold their effects. However, the specific signaling events and/or physiological effects clearly attributable to the estradiol content in HDL particles have not been unequiv-ocally defined. In one study, HDL-associated estradiol was found to stimulate eNOS and vasodilation in an SR-BI- and Akt-dependent manner, but these results were questioned by others (Gong et al. 2003; Nofer et al. 2004). In other study, dehydroepiandrosterone (DHEA) fatty acyl esters once incorporated in HDL were found to induce stronger vasodilatory response, and this effect appeared also to be mediated by SR-BI (Paatela et al. 2011). However, no clear signaling link between the HDL-associated DHEA and vasodilation has been established in this study. These two examples clearly show that the assignment of ligands present in HDL to the appending signaling machinery and to various functions exerted by these lipoproteins in physiology will be a major challenge in the future.

The composition of HDL particles is variable and influenced both by normal metabolism and in various states of pathology. For instance, HDL particles isolated from subjects suffering from acute or chronic inflammatory diseases were found to lose proteins and enzymes with established or presumed antiatherogenic function such as apoA-I or LCAT and to concomitantly acquire proinflammatory or prooxidative factors such as serum amyloid A (SAA), ceruloplasmin, lipoprotein-specific phospholipase A_2, or myeloperoxidase. Not surprisingly, such inflamma-tory HDL particles are severely impeded in their capacity to trigger certain signal-ing pathways, but at the same time may acquire new ligands and thereby alter their signaling properties. For instance, the relatively high content of apolipoprotein J (apoJ) in HDL particles obtained from healthy subjects endowed them with impor-tant antiatherogenic property to promote endothelial survival by stimulation of the expression of antiapoptotic protein Bcl-XL (Riwanto et al. 2013). By contrast, HDL particles isolated from patients with stable coronary heart disease (CHD) or acute coronary syndromes were found to be poor in apoJ, but instead enriched in apoC-I or apoC-III (McNeal et al. 2013; Riwanto et al. 2013). Furthermore, the increased content of these apolipoproteins turned HDL particles into potent apoptosis inducers in vascular smooth muscle and endothelial cells by virtue of stimulating the expression of proapoptotic protein tBid. In addition to CHD, dysfunctional HDL is also encountered in chronic conditions such as chronic kidney disease (CKD). Abnormal HDL composition characterized primarily by increased serum amyloid A and apoC-III content as well as compromised HDL functionality has been repeat-edly reported in uremic patients (Holzer et al. 2011; Weichhart et al. 2012). In one recent study, SAA-enriched HDL encountered in CKD was found to induce pro-duction of a proinflammatory chemokine MCP1 in smooth muscle cells by interac-tion with formyl peptide receptor 2 (FPR2) (Tölle et al. 2012). In other study conducted in CKD patients, accumulation of symmetric dimethylarginine (SDMA) in HDL was found to turn this lipoprotein into a noxious particle reducing NO bioavailability, evoking endothelial dysfunction, and subsequently increasing arterial blood pressure. The deleterious effects of SDMA-modified HDL were attributed to the noncanonical activation of TLR2 (Speer et al. 2013). This exemplifies another challenge facing HDL research in the future, namely,

identification of ligands, receptors, and signaling cascades attributable to HDL in various states of pathology.

Notwithstanding the physiological or pathological character of HDL-induced signal transduction, its elucidation may open new opportunities for the development of antiatherogenic, anti-inflammatory, or antithrombotic drugs. Several interventional studies conducted recently and aiming at cardiovascular risk reduction through simple elevation of plasma HDL cholesterol fall through. This epic failure emphasizes the necessity to develop more sophisticated strategies based on targeted exploitation of selected antiatherogenic or anti-inflammatory activities exerted by HDL particles. The proper understanding of HDL-induced signaling may help to specifically enhance beneficial physiological or to disable harmful pathological effects of HDL and thereby to design more efficacious therapeutic approaches for cardiovascular and other inflammatory diseases.

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