

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,100

Open access books available

116,000

International authors and editors

120M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Pleiotropic Functions of HDL Lead to Protection from Atherosclerosis and Other Diseases

Vassilis Zannis^{1,2}, Andreas Kateifides^{1,2}, Panagiotis Fotakis^{1,2},
Eleni Zanni¹ and Dimitris Kardassis²

¹*Molecular Genetics, Boston University School of Medicine Boston, MA,*

²*University of Crete Medical School, Greece,*

¹USA

²Greece

1. Introduction

High density lipoprotein (HDL) is a macromolecular complex of proteins and lipids that is produced primarily by the liver through a complex pathway that requires initially the functions of apolipoprotein A-I (apoA-I), ATP binding cassette transporter A1 (ABCA1) and lecithin:cholesterol acetyl transferase (LCAT) (Zannis et al., 2006b). Following synthesis, HDL affects the functions of the arterial wall cells through signaling mechanisms mediated by scavenger receptor class B type-I (SR-BI) and other cell surface proteins. The impetus for studying HDL has been the inverse correlation that exists between plasma HDL levels and the risk for coronary artery disease (CAD) (Gordon et al., 1989). HDL promotes cholesterol efflux (Gu et al., 2000; Nakamura et al., 2004), prevents oxidation of low density lipoprotein (LDL) (Navab et al., 2000a; Navab et al., 2000b), inhibits expression of proinflammatory cytokines by macrophages (Okura et al., 2010) as well as expression of adhesion molecules by endothelial cells (Cockerill et al., 1995; Nicholls et al., 2005b). HDL inhibits cell apoptosis (Nofer et al., 2001) and promotes endothelial cell proliferation and migration (Seetharam et al., 2006). HDL stimulates release of nitric oxide (NO) from endothelial cells thus promoting vasodilation (Mineo et al., 2003). HDL also inhibits platelet aggregation and thrombosis (Dole et al., 2008) and has antibacterial, antiparasitic and antiviral activities (Parker et al., 1995; Singh et al., 1999; Vanhollebeke and Pays, 2010). Due to these properties HDL is thought to protect the endothelium and inhibit several steps in the cascade of events that lead to the pathogenesis of atherosclerosis and various other human diseases.

This review focuses on two important aspects of contemporary HDL research. The first part considers briefly the structure of apoA-I and HDL and the key proteins that participate in the pathway of the biogenesis of HDL as well as clinical phenotypes associated with HDL abnormalities. The second part considers various physiological functions of HDL and apoA-I and the protective role of HDL against atherosclerosis and other diseases.

2. Biogenesis of HDL

HDL is synthesized through a complex pathway (Zannis et al., 2004a). The first step involves an ABCA1 mediated transfer of cellular phospholipids and cholesterol to lipid poor apoA-I extracellularly. The lipidated apoA-I is gradually converted to discoidal particles that are remodelled in the plasma compartment by the esterification of cholesterol by the enzyme LCAT (Zannis et al., 2006a) and are converted to spherical HDL particles. The cholesteryl esters formed are transferred to very low-density lipoproteins/intermediate-density lipoproteins/low density lipoproteins (VLDL/IDL/LDL) by the cholesteryl ester transfer protein (CETP) (Barter et al., 2003). Additional remodeling of HDL involves transfer of phospholipids from VLDL/IDL to HDL by the phospholipid transfer protein (PLTP) (Lusa et al., 1996), cholesterol efflux from cells or delivery of cholesteryl esters to cells mediated by the SR-BI (Krieger, 2001) as well as cholesterol efflux mediated by the cell surface transporter ATP binding cassette transporter G1 (ABCG1) (Wang et al., 2004). Finally hydrolysis of lipids of HDL is mediated by various lipases [lipoprotein lipase (LpL), hepatic lipase (HL), endothelial lipase (EL)] (Breckenridge et al., 1982; Brunzell and Deeb, 2001; Ishida et al., 2003; Krauss et al., 1974). Mutations in any of these proteins may affect the biogenesis, maturation and the functions of HDL (Fig. 1).

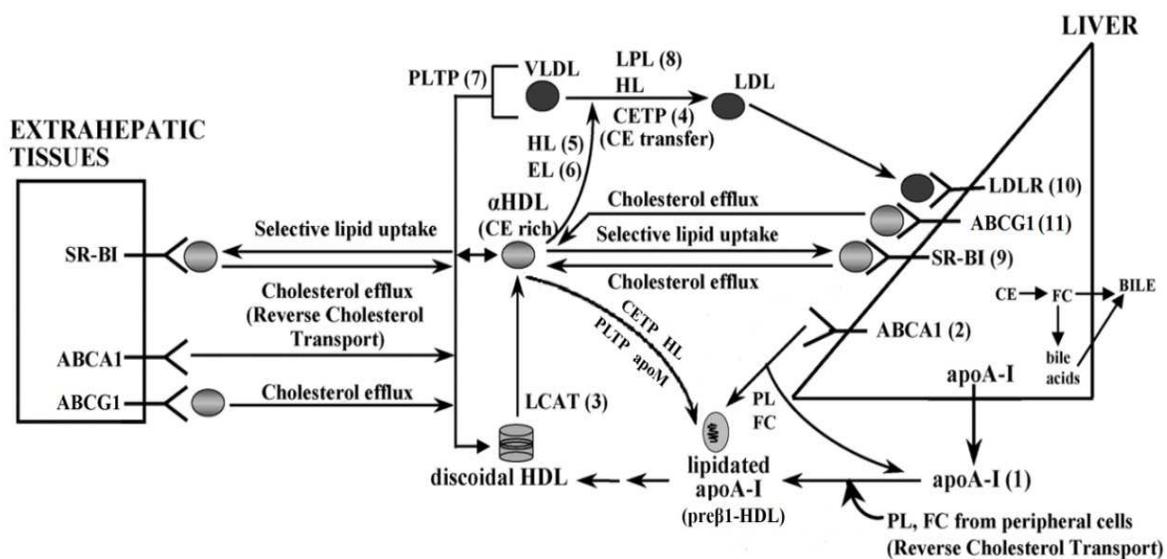


Fig. 1. Schematic representation of the pathway of the biogenesis and catabolism of HDL. Numbers 1-11 indicate key cell membrane or plasma proteins shown to influence HDL levels or composition as follows: 1) apoA-I; 2) ABCA1; 3) LCAT; 4) CETP; 5) HL; 6) EL; 7) PLTP; 8) lipoproteins lipase; 9) SR-BI; 10) LDL receptor; 11) ABCG1. The figure is modified from ref. (Zannis et al., 2004b; Zannis et al., 2006b).

3. Proteins involved in the biogenesis, remodeling and signaling of HDL

3.1 Apolipoprotein A-I and its structure in solution and in discoidal and spherical HDL

ApoA-I is synthesized by the liver and the intestine in humans (Williamson et al., 1992) and it is the major protein component of the HDL. ApoA-I along with several other proteins participate in the biogenesis and remodeling of HDL as well as in signaling pathways induced by apoA-I and HDL (Yuhanna et al., 2001; Zannis et al., 2004a). ApoA-I contains 22 or 11

amino acid repeats which are organized in amphipathic α -helices (Nolte and Atkinson, 1992). Based on the crystal structure of apoA-I in solution (Borhani et al., 1997) a belt model was proposed to explain the structure of apoA-I on discoidal HDL particles. In this model, two antiparallel molecules of apoA-I are wrapped like a belt around a discoidal bilayer containing 160 phospholipid molecules and shields the hydrophobic fatty acid chains of the phospholipids. Analysis of the 93 Å spherical HDL in solution by small angle neutron scattering (SANS) showed that three molecules of apoA-I fold around a central lipid core that has 88.4 Å x 62.8 Å dimensions to form a spheroidal HDL (sHDL) particle (Wu et al., 2011).

3.2 Interactions of ApoA-I with ABCA1 are the first step in the biogenesis of HDL

ABCA1 is a ubiquitous protein that belongs to the ABC family of transporters and is expressed abundantly in the liver, macrophages, brain and various other tissues (Kielar et al., 2001). ABCA1 was shown to promote the efflux of cellular phospholipids and cholesterol to lipid free or minimally lipidated apoA-I and other apolipoproteins and amphipathic peptides, but it does not promote efflux to spherical HDL particles (Remaley et al., 2001; Wang et al., 2000). The functional interactions between apoA-I and ABCA-1 are important for the biogenesis of HDL. In the absence of either apoA-I (Matsunaga et al., 1991) or ABCA-1 (Brunham et al., 2006) HDL is not formed. Adenovirus mediated gene transfer of apoA-I mutants in apoA-I^{-/-} mice showed that deletion of the C-terminal region of apoA-I prevented the formation of HDL (Chroni et al., 2007). The ability of ABCA1 to promote cholesterol efflux from macrophages is very important for the prevention of formation of foam cells in the atherosclerotic lesions (Van Eck et al., 2002). Mutations resulting in inactivation of ABCA1 are present in patients with Tangier disease (Brunham et al., 2006). The deficiency is associated with very low levels of total plasma and HDL cholesterol and abnormal lipid deposition in various tissues (Christiansen-Weber et al., 2000; McNeish et al., 2000). The ABCA1 deficiency in humans or experimental animals may contribute to accelerated atherosclerosis (Joyce et al., 2002; Singaraja et al., 2003). Inactivation of the ABCA1 gene in macrophages increases the susceptibility to atherosclerosis (Van Eck et al., 2002; Van Eck et al., 2006). Specific amino acid substitutions found in the Danish general population were predictors of ischemic heart disease and reduced life expectancy (Frikke-Schmidt et al., 2008).

3.3 Interactions of lipid-bound ApoA-I with LCAT stabilize the nascent HDL

Plasma LCAT is a 416 amino acid long enzyme that is synthesized and secreted by the liver and esterifies the free cholesterol of HDL and LDL. ApoA-I is a potent activator of LCAT (Fielding et al., 1972). Following esterification, the cholesteryl esters formed become part of the lipid core and the discoidal HDL is converted to mature spherical HDL (Chroni et al., 2005a).

Mutations in LCAT are associated with two phenotypes in humans. The familiar LCAT deficiency (FLD) is characterized by the inability of the mutant LCAT to esterify cholesterol on HDL and LDL and causes accumulation of discoidal HDL in the plasma. The fish eye disease (FED) is characterized by the inability of mutant LCAT to esterify cholesterol on HDL only. Both diseases are characterized by low HDL levels due to the inability of LCAT to convert the nascent immature pre- β and discoidal particles to mature spherical HDL (Santamarina-Fojo et al., 2001).

3.4 Interactions of lipid-bound ApoA-I with SR-BI

SR-BI is an 82 kDa membrane glycoprotein primarily expressed in the liver, steroidogenic tissues and endothelial cells but is also found in other tissues. The most important property of SR-BI is considered to be its ability to act as the HDL receptor (Acton et al., 1996). SR-BI mediates both selective uptake of cholesteryl esters and other lipids from HDL to cells (Acton et al., 1996; Stangl et al., 1999; Thuahnai et al., 2001), as well as efflux of unesterified cholesterol (Gu et al., 2000). Transgenic mice expressing SR-BI in the liver had greatly decreased apoA-I and HDL levels as well as increased clearance of VLDL and LDL (Ueda et al., 1999) and were protected from atherosclerosis (Arai et al., 1999). SR-BI deficient mice had decreased HDL cholesterol clearance (Out et al., 2004), two fold increased plasma cholesterol and presence of large size abnormal apolipoprotein E (apoE) enriched particles that were distributed in the HDL/IDL/LDL region (Rigotti et al., 1997). The SR-BI deficiency in the background of LDL receptor (LDLr) deficient or apoE deficient mice accelerated dramatically the development of atherosclerosis (Huszar et al., 2000; Trigatti et al., 1999). The double deficient mice for apoE and SR-BI developed occlusive coronary atherosclerosis, cardiac hypertrophy, myocardial infarctions, cardiac dysfunction and died prematurely (mean age of death ~6 weeks) (Braun et al., 2002; Trigatti et al., 1999). The SR-BI deficiency reduced greatly cholesteryl ester levels in the steroidogenic tissues that utilize HDL cholesterol for synthesis of steroid hormones (Ji et al., 1999). It also decreased secretion of biliary cholesterol by approximately 50% (Mardones et al., 2001; Rigotti et al., 1997). The SR-BI deficiency also caused defective maturation of oocytes and red blood cells due to accumulation of cholesterol in the plasma membrane of progenitor cells (Holm et al., 2002; Trigatti et al., 1999) and caused infertility in the female but not the male mice (Trigatti et al., 1999; Yesilaltay et al., 2006). Interactions of HDL with SR-BI in endothelial cells triggers signaling mechanisms discussed below that involve activation of endothelial nitric oxide synthase (eNOS) and release of NO that causes vasodilation (Mineo et al., 2003; Yuhanna et al., 2001). Human subjects have been identified with a P297S substitution in SR-BI. Heterozygote carriers for this mutation had increased HDL levels, decreased adrenal steroidogenesis and dysfunctional platelets but did not develop atherosclerosis (Vergeer et al., 2011).

A [Gly2Ser]SR-BI substitution in humans is associated with decreased follicular progesterone levels in Caucasian women and non viable fetuses 42 days post embryo transfer. Another single nucleotide polymorphism (SNP) (rs10846744) was associated with gestational sacs and fetal heart beats and with poor fetal viability in African-American women (Yates et al., 2011).

3.5 Interactions of HDL with ABCG1

ABCG1 is a 67 kDa protein which is a member of ABC family of half transporters. ABCG1 is expressed in the spleen, thymus, lung, brain, endothelial cells and other tissues (Savary et al., 1996) and promotes cholesterol efflux from cells to HDL but not to lipid free apoA-I (Nakamura et al., 2004; Vaughan and Oram, 2005). The absence of ABCG1 in mice causes cholesterol accumulation in various tissues (Kennedy et al., 2005) and selective deletion of both ABCA1 and ABCG1 genes in macrophages further increases cholesterol accumulation and results in severe atherosclerosis (Out et al., 2008; Yvan-Charvet et al., 2007).

4. Phenotypes of humans and experimental animals having apoA-I mutations

4.1 Natural apoA-I mutations

Several apoA-I mutations have been described in the general population that are associated with low plasma HDL levels. Most of the mutations affect the interaction of apoA-I with LCAT. Eight mutations between residues 26 and 107 and one on residue 173, have been associated with amyloidosis and low HDL levels (Sorci-Thomas and Thomas, 2002; Zannis et al., 1993) and one mutation on residue 164 is associated with increased risk for ischemic heart disease and reduced life expectancy (Haase et al., 2011). The *in vivo* interactions of representative naturally occurring apoA-I mutants with LCAT were studied by adenovirus-mediated gene transfer in apoA-I deficient mice. The mutants apoA-I(Leu141Arg)_{Pisa} and apoA-I(Leu159Arg)_{FIN} produced only small amounts of HDL that formed mostly pre β 1 and small size α 4 HDL particles. The apoA-I(Arg151Cys)_{Paris} and apoA-I(arg160Leu)_{Oslo} formed discoidal HDL particles. These studies indicated that apoA-I(Leu141Arg)_{Pisa} and apoA-I(Leu159Arg)_{FIN} mutation may inhibit an early step in the biogenesis of HDL due to insufficient esterification of the cholesterol of the pre β 1-HDL particles by the endogenous LCAT. The LCAT insufficiency appears to result from depletion of the plasma LCAT mass (Koukos et al., 2007). A remarkable finding of these studies was that all the aberrant phenotypes were corrected by treatment with exogenous LCAT. This indicates that LCAT administration could be a potential therapeutic intervention to correct low-HDL conditions in humans that are caused by these and other unidentified mutations (Amar et al., 2009).

4.2 Specific bioengineered mutations in ApoA-I may cause dyslipidemia

Four bioengineered mutations in apoA-I have been studied by adenovirus-mediated gene transfer in apoA-I deficient mice. Mutants apoA-I[Δ (62-78)], apoA-I [Glu110Ala/Glu111Ala] and apoA-I[Asp89Ala/Glu90Ala/Glu92Ala], caused combined hyperlipidemia, characterized by elevated plasma cholesterol and severe hypertriglyceridemia (Chroni et al., 2004; Chroni et al., 2005b; Kateifides et al., 2011). An apoA-I[Δ 89-99] mutant induced high plasma cholesterol, but did not affect plasma triglyceride levels (Chroni et al., 2005b).

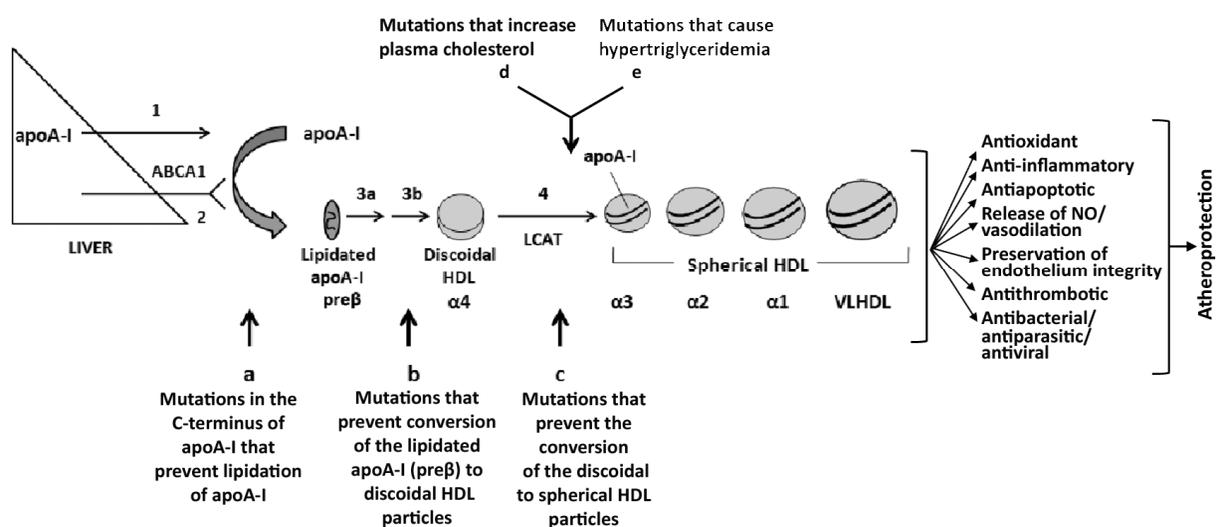


Fig. 2. The pathway of HDL biogenesis and functions of HDL. a-e represent sites of possible disruption of the HDL biogenesis pathway. Different subpopulations of HDL that have been generated due to these defects may have different functions.

The systematic study of the functions of apoA-I by adenovirus mediated gene transfer as well as the phenotypes of naturally occurring apoA-I mutants identified the following five steps where the pathway of biogenesis and/or catabolism of HDL can be disrupted: a) Lack of synthesis of HDL due to mutations in ABCA1 or mutations in apoA-I that affect the ABCA1/apoA-I interaction, b) Failure to convert efficiently the lipidated pre- β HDL to discoidal HDL. This defect most likely results from fast catabolism of apoA-I following its lipidation by ABCA1, c) Accumulation of discoidal HDL. This phenotype has been generated by the mutations in the 149-160 region of apoA-I that affect LCAT activation, d) Accumulation of discoidal HDL and induction of hypercholesterolemia. This condition has been observed in the case of the apoA-I[Δ (89-99)] mutant, e) Induction of hypertriglyceridemia. This defect has been observed in the case of apoA-I[Δ (62-78)], apoA-I[Glu110Ala/Glu111Ala] and apoA-I[Asp89Ala/Glu90Ala/Glu92Ala] mutants (Fig. 2).

5. Physiological functions of ApoA-I and HDL that may be relevant to its atheroprotective properties

5.1 Cell signaling pathways mediated by HDL and apoA-I

Various studies have shown that increased HDL levels are associated with greater vasodilator effects in humans and this effect is impaired in patients with coronary heart disease (CHD) (Li et al., 2000; Zeiher et al., 1994). Treatment with HDL increased eNOS protein levels in cultured human aortic endothelial cells (HAECs) (Ramet et al., 2003). Other studies in endothelial cells and Chinese hamster ovary (CHO) cells that express SR-BI, showed that SR-BI-HDL interactions lead to the phosphorylation and activation of eNOS. The HDL-induced eNOS activation occurs in the caveolae. The HDL-mediated NO-dependent relaxation is lost in aortic rings of SR-BI^{-/-} mice (Yuhanna et al., 2001). Experiments in cultures of endothelial cells and COS M6 cells transfected with eNOS and SR-BI showed that interaction of HDL with SR-BI triggered signalling mechanisms which led to phosphorylation of eNOS at Ser1179 and increased its activity. On the other hand phosphorylation of Thr 497 of eNOS attenuated its activity. The signalling cascade initially involves the nonreceptor tyrosine kinase Src which phosphorylated PI3 kinase (PI3K). Inhibition of Src by specific inhibitors prevented eNOS phosphorylation. PI3K activation led to phosphorylation of Akt and mitogen-activated protein kinase (MAPK) which independently phosphorylated eNOS. Inhibitors of MAPK did not affect HDL-mediated Akt activation and a dominant negative Akt did not affect HDL-mediated MAPK activation and eNOS phosphorylation (Mineo et al., 2003) (figure 3A).

The mechanism of the SR-BI mediated activation of eNOS was studied in detail (Assanasen et al., 2005). HDL and cholesterol-free reconstituted HDL (rHDL) particles containing apoA-I and phosphatidylcholine (Lp2A-I) as well as cyclodextrin stimulated eNOS activity whereas rHDL particles that contain cholesterol did not. Blocking of cholesterol efflux with a monoclonal antibody to SR-BI abolished the activation of eNOS. Experiments were performed using SR-BII, a splice variant of SR-BI as well as a SR-BI mutant that lacks the carboxyterminal amino acid 509 [SR-BI(Δ 509)] and chimeric receptors where the transmembrane and the C-terminal domains of SR-BI were replaced by the corresponding domains of CD36. These studies established that the C-terminal cytoplasmic PDZ-interacting domain and the C-terminal transmembrane domain of SR-BI were both required for eNOS activation (Assanasen et al., 2005). The cytoplasmic PDZK1 interacting domain of SR-BI binds adaptor proteins such as PDZK1 that may participate in cell signalling (Kocher

et al., 2003). A photoactive derivative of cholesterol binds in the transmembrane region of SR-BI indicating that this region serves as a cholesterol sensor on the plasma membrane (Assanasen et al., 2005). HDL and lysophospholipids that are components of HDL including sphingosylphosphorylcholine, sphingosine-1-phosphate (S1P) and lysosulphatide cause eNOS dependent relaxation of mouse aortic rings via intracellular Ca^{2+} mobilization and eNOS phosphorylation mediated by Akt (Nofer et al., 2004). Another study however, indicated that interactions of HDL with SR-BI stimulate eNOS by increasing intracellular ceramide levels without affecting intracellular calcium levels and Akt phosphorylation (Li et al., 2002). The proposed role of HDL-associated estradiol in the stimulation of eNOS activity is unclear (Gong et al., 2003). 5' AMP-activated protein kinase (AMPK) may also play a role in the HDL-mediated phosphorylation of eNOS at multiple sites (Ser116, Ser635, and Ser1179) (Drew et al., 2004). It was suggested that activation by AMPK may involve physical interactions between the apoA-I component of HDL and eNOS. Such interactions may be possible following SR-BI mediated endocytosis of HDL (Silver et al., 2001). HDL also affected the signaling in endothelial cells by the bone morphogenetic protein 4 (BMP4) and increased expression of the activin-like kinase receptor 1 and 2 (Yao et al., 2008). This resulted in increased expression of vascular endothelial growth factor (VEGF) and matrix gla protein (MGP). VEGF promotes endothelial cell survival and MGP prevents vascular calcification and thus contribute to the maintenance, the integrity and the preservation of the functions of the endothelium (Yao et al., 2008).

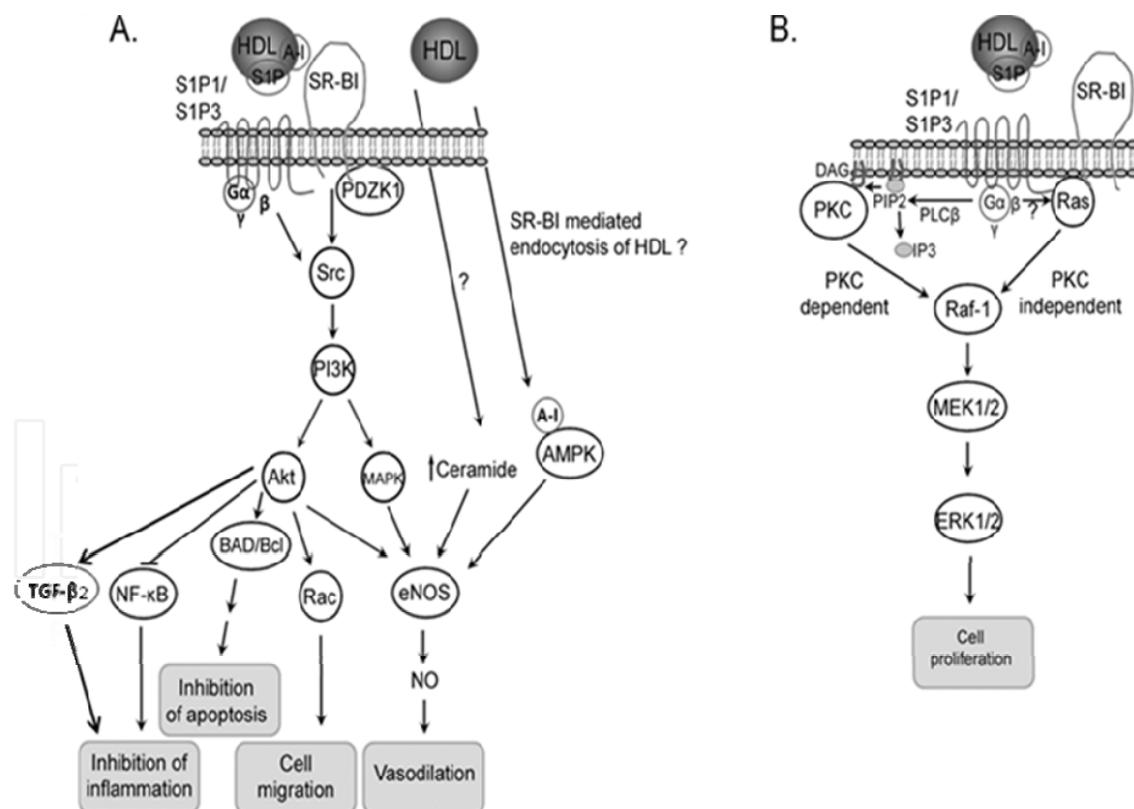


Fig. 3. A) Schematic representation of SR-BI signaling that can lead to vasodilation, cell migration and inhibition of inflammation and apoptosis. B) Schematic representation of PKC-dependent SR-BI-dependent signalling pathway that promote cell proliferation (Drew et al., 2004; Grewal et al., 2003; Kimura et al., 2003; Mineo et al., 2003).

5.2 Effect of HDL and apoA-I on inflammation

An initial step in the pathogenesis of atherosclerosis is the association of the monocytes to adhesion molecules of the endothelial cells that facilitates their entry in the sub-endothelial space (Zannis et al., 2004b). Induction of adhesion molecules is promoted by pro-inflammatory stimuli (Cybulsky and Gimbrone, Jr., 1991). Recruitment and migration of monocytes into sub-endothelial space is promoted by the monocyte chemoattractant factor (MCP-1) as well as by oxidized LDL (Peters and Charo, 2001). HDL has anti-oxidant properties and can prevent the oxidation of LDL (Navab et al., 2000a; Navab et al., 2000b). Interactions of HDL or apoA-I with cells of the vascular wall were shown to prevent the expression of pro-inflammatory cytokines and chemokines that induce the expression of adhesion molecules (Bursill et al., 2010; Cockerill et al., 1995; Nobecourt et al., 2010). The anti-inflammatory functions of HDL were manifested in several ways. HDL binds via its apoA-I moiety to progranulin produced by macrophages. This prevents conversion of progranulin to inflammatory granulins which were shown to induce expression of tumor necrosis factor α (TNF α) and interleukin (IL) 1 β in monocyte macrophages (Okura et al., 2010). HDL and rHDL were shown to inhibit the cytokine induced expression of vascular cell adhesion molecule-1 (VCAM-1) and inter-cellular adhesion molecule-1 (ICAM-1) by endothelial cells (Cockerill et al., 1995). In addition, HDL promoted the expression of anti-inflammatory cytokines in endothelial cells. Thus treatment of endothelial cells (HUVEC) with HDL and lysosphingolipids present in HDL, increased the expression of TGF- β ₂ through mechanisms that involve the activation of Akt and extracellular signal regulated kinases (ERK) 1/2. Consistent with cell culture studies, the expression of transforming growth factor- β ₂ (TGF- β ₂) and the phosphorylation of ERK1/2, Akt and Smad2/3 were increased in apoA-I transgenic mice and diminished in apoA-I deficient mice (Norata et al., 2005). In vivo studies also showed that infusion of rHDL inhibited the pro-oxidant and pro-inflammatory events that occurred following implantation of non occlusive periarterial collars in rabbits that induce acute arterial inflammation. In these studies the rHDL inhibited neutrophil infiltration, production of reactive oxygen species (ROS) and the expression of VCAM-1, ICAM-1, MCP-1 and E-selectin (Nicholls et al., 2005b). The carotid vascular inflammation and neutrophil infiltration could be inhibited by rHDL containing normal apoA-I but not by apoA-I obtained from diabetic patients (Nobecourt et al., 2010). The beneficial effects of rHDL containing apoA-I in vivo and in cell cultures could be duplicated using synthetic apoA-I mimetics such as 5A, L37pA and D37pA (Gomaschi et al., 2008; Tabet et al., 2010). The 5A/PLPC complexes reduced the vascular inflammation that is associated with collar insertion in a rabbit model by reducing the ICAM-1 and VCAM-1 expression, the infiltration of neutrophils and the Nox4 activity. In cultures of human carotid endothelial cells (HCEC) 5A/PLPC and rHDL containing apoA-I inhibited the TNF- α induced VCAM-1 and ICAM-1 expression as well as the activation of nuclear factor κ B (NF- κ B) pathway and these effects were abolished by ABCA1 silencing (Tablet et al., 2010). Complexes of L37pA or D37pA with β -oleoyl- γ -palmitoyl-L- α -phosphatidylcholine reduced the postischemic cardiac contractile dysfunction in a rat heart model of ischemia/reperfusion. They also reduced TNF- α levels and increased prostacyclin levels in the perfusate and inhibited the TNF- α mediated VCAM-1 expression in endothelial cell cultures (Gomaschi et al., 2008). In monocyte and endothelial cell cultures HDL also suppressed expression of chemokines CCL2, CCL5 and CX3CL1 and chemokine receptors CCR2, CCR5 and CX3CR1 (Bursill et al., 2010). This effect was mediated by inhibition of I κ -

B α phosphorylation and NF- κ B(p65) expression and in some cases by peroxisome proliferator-activated receptor γ (PPAR γ) activation. Consistent with cell culture studies, in vivo infusion of apoA-I in cholesterol fed apoE deficient mice reduced expression of chemokines and chemokine receptors (Bursill et al., 2010). HDL and its protein moiety apoA-I have been shown to inhibit the expression of CD11b of human monocytes that is induced by phorbol myristate acetate (PMA) and promote cell adhesion. Inhibition of the ABCA1-mediated and to a lesser extent SR-BI mediated cholesterol efflux by monoclonal antibodies attenuated the inhibitory effect of apoA-I and HDL respectively. Expression of CD11b was also affected by depletion of the membrane cholesterol by treatment of the cells with cyclodextrin (Murphy et al., 2008), pointing out to a potential role of cholesterol efflux in the inhibition of inflammation. Consistent with the ex vivo studies infusion of rHDL in patients with type 2 diabetes mellitus, reduced the expression of CD11b of the peripheral monocytes and reduced the adhesion of the patients' neutrophils to a fibrinogen matrix. Plasma HDL isolated 4 to 72 hours post rHDL infusion suppressed the expression of VCAM-1 in cultures of HAECs and had increased ability to promote cholesterol efflux from THP-1 macrophages (Patel et al., 2009). In cultures of smooth muscle cells, HDL downregulated the NADPH-oxidase mediated generation of reactive oxygen species (ROS) and inhibited production of MCP-1. The inhibitory effect was attenuated by antagonists of S1P₁ and S1P₃ receptors. The data showed that free S1P or S3P alone or as components of HDL could attenuate production of MCP-1. Consistent with these findings, MCP-1 production and ROS generation in the aortas of S1P₃^{-/-} receptor and SR-BI^{-/-} mice were not affected by treatment with HDL, S1P and sphingosylphosphorylcholine (SPC) (Tolle et al., 2008). ApoA-I induced the expression of the adhesion molecule CD31, and changed the morphology and size distribution of lineage negative bone marrow cells. The treatment also increased the ability of the cells to bind to fibronectin and to cultured endothelial cells. Deletion of the C-terminal helix 10 of apoA-I abolished the effects of apoA-I on bone marrow cells (Myhre et al., 2008).

5.3 Effect of HDL and apoA-I on endothelial cell apoptosis

Exposure of endothelial cells to inflammatory stimuli may disturb the endothelial monolayer integrity (Dimmeler et al., 2002). Numerous factors that promote endothelial apoptosis have been described and include OxLDL (Li et al., 1998), TNF- α (Dimmeler et al., 1999), homocysteine (Welch and Loscalzo, 1998), and angiotensin II (Strawn and Ferrario, 2002). HDL also can reverse the TNF- α induced and growth deprivation induced endothelial cell apoptosis (Nofer et al., 2001; Sugano et al., 2000). OxLDL increased intracellular calcium and resulted in apoptosis that could be inhibited by HDL and apoA-I (Suc et al., 1997). ApoA-I interacts with ABCA1 and F1-ATPase (Chroni et al., 2003; Vantourout et al., 2010), whereas HDL interacts with SR-BI and ABCG1 (Liadaki et al., 2000; Wang et al., 2004) respectively and the sphingolipid components of HDL interact with the S1P receptors (Kimura et al., 2003; Okajima et al., 2009). HDL protected endothelial cells from apoptosis induced by oxLDL by preventing the generation of intracellular ROS. The anti-apoptotic activity was highest for HDL₃ and diminished as the size of HDL increased. It was suggested that approximately 70% of the anti-apoptotic activity of HDL was attributed to apoA-I which has the capacity to accept through its methionine residues the phospholipid hydroperoxides (PLOOH) of oxLDL (de Souza et al., 2010). The anti-apoptotic functions of small size HDL₃ was reduced by 35% in subjects with metabolic syndrome and this

reduction was correlated with the clinical phenotype of the human subjects. Compared to normal HDL the HDL₃ fractions of the diabetic subjects had increased total triglyceride levels and decreased cholesteryl esters/triglycerides ratio suggesting that the lipid core of HDL₃ was enriched with triglycerides (de Souza et al., 2008). HDL₃ also inhibited apoptotic cell death induced by oxLDL and preserved lysosomal integrity of an osteoblastic cell line (Brodeur et al., 2008). The anti-apoptotic effects were attributed to the increased expression of SR-BI that is mediated by HDL₃, combined with the ability of HDL to compete for the binding of oxLDL to osteoblasts as well as increased selective uptake of the cholesterol of the oxLDL by these cells (Brodeur et al., 2008).

Interactions of apoA-I with cell surface F1-ATPase inhibited apoptosis of HUVEC and stimulated cell proliferation (Radojkovic et al., 2009). In the absence of apoA-I, specific inhibitors for F1-ATPase (IF₁-H49K) and angiostatin or specific antibodies to F1-ATPase promoted apoptosis and inhibited cell proliferation. In the presence of apoA-I, F1-ATPase inhibitors and antibodies diminished its anti-apoptotic and anti-proliferative effects. Down-regulation of the ABCA1 by siRNA did not affect the anti-apoptotic and proliferative functions of apoA-I whereas inhibition of SR-BI by a specific antibody diminished the anti-apoptotic and proliferative functions of HDL₃ (Radojkovic et al., 2009). The findings suggest that interactions of lipid free apoA-I with F1-ATPase and of HDL with SR-BI contribute to their anti-apoptotic and proliferative effects on endothelial cells. The antiapoptotic effects of HDL on endothelial cells could be mimicked by the lysosphingolipid components of HDL (Nofer et al., 2001). The SR-BI mediated signalling that leads to activation of eNOS, also promotes cell growth and migration and protects cells from apoptosis (Mineo et al., 2006; Noor et al., 2007). Activation of eNOS required its localization in the caveolae, where caveolin SR-BI and CD36 are also found (Uittenbogaard et al., 2000). It has been proposed that oxLDL acting through CD36 depletes the cholesterol content of caveolae and leads to eNOS redistribution to intracellular sites thus resulting in decreased eNOS activity (Blair et al., 1999; Uittenbogaard et al., 2000). HDL acting through SR-BI maintains the concentration of caveolae-associated cholesterol, inhibits the actions of oxLDL and maintains eNOS in the caveolae (Uittenbogaard et al., 2000). This interpretation implies that strong interactions between eNOS and caveolin-1 (Cav-1) stimulate eNOS activity. Other studies provided the opposite mechanism of modulation of eNOS activity by interactions of eNOS with Cav-1 (Terasaka et al., 2010). It was shown that these interactions were enhanced by loading cells with cholesterol or oxysterols and decreased by cholesterol depletion in endothelial cells as a result of ABCG1-mediated cholesterol efflux. Studies in murine lung endothelial cells (MLEC) also showed that HDL could reverse the inhibition of eNOS activity caused by cholesterol loading in the normal but not the Cav-1 deficient cells (Terasaka et al., 2010). It was proposed that diminished interactions between eNOS and Cav-1 caused by ABCG1-mediated efflux stimulated eNOS activity. It has been shown that oxidized phospholipids uncouple eNOS activity and lead to the generation of oxygen radicals which induces the expression of sterol regulatory element binding protein (SREBP) and IL-8 (Gharavi et al., 2006; Yeh et al., 2004). ApoA-I mimetic peptides also prevent LDL from uncoupling eNOS activity to favour O₂⁻ anion production as opposed to normal production of NO (Ou et al., 2003). Finally it has been shown that SR-BI via a highly conserved redox motif CXXS between residues 323-326 can promote a ligand independent apoptosis via a caspase 8 pathway and this effect could be reversed by HDL and eNOS (Li et al., 2005). It was proposed that at low HDL levels oxidative stress causes relocation of eNOS away from the

caveolae and this results in SR-BI induced apoptosis (Li et al., 2005). The picture that emerges from these studies is that HDL promotes survival and migration of endothelial cells by signalling mechanisms that originate from the interactions of HDL with SR-BI, the interactions of S1P with S1P1 and S1P3 receptors and the interactions of lipid-free apoA-I with F1-ATPase.

5.4 Effect of HDL on endothelial cell proliferation and migration

Damage of the endothelium is associated with vascular disease which can be blunted by re-endothelialization (Werner et al., 2003). HDL promoted proliferation of HUVEC via mechanisms that increased intracellular Ca^{2+} and upregulated the production of prostacyclin (Tamagaki et al., 1996). HDL also promoted endothelial cell migration (Murugesan et al., 1994). Migration was promoted by signalling cascades mediated by interaction of S1P with S1P1 and S1P3 receptors that led to the activation of PI3 kinase, p38MAP kinase and Rho kinases (Kimura et al., 2003). Other studies showed that HDL can activate the MAPK pathway either through processes that involve protein kinase C (PKC), Raf-1, MEK and ERK1/2 or PKC independent pathways. This latter pathway leads to the activation of Ras and can be inhibited by pertussis toxin and neutralizing antibodies against SR-BI (Grewal et al., 2003). The data suggest that interactions of HDL with SR-BI activate Ras in a PKC independent manner and this leads to subsequent activation of MAPK signalling cascade (Grewal et al., 2003) (Fig.3B). Another beneficial effect of HDL is its capacity to promote capillary tube formation *in vitro*. This function is pertussis toxin sensitive and requires p44/42MAP kinase which is downstream of Ras (Miura et al., 2003). Other studies showed that interaction of SR-BI with HDL or rHDL, activated Src kinases and Rac GTPases and stimulated endothelial cell migration. *In vivo* experiments have also shown that re-endothelialization of carotid artery following injury is promoted by apoA-I expression and is inhibited in apoA-I deficient mice (Seetharam et al., 2006).

5.5 Effect of HDL on thrombosis

Increased HDL cholesterol levels are associated with decreased risk of venous thrombosis (Doggen et al., 2004). In contrast low HDL levels are associated with increased risk of venous thrombosis (Deguchi et al., 2005). The ability of HDL to inhibit endothelial cell apoptosis (Dimmeler et al., 2002; Mineo et al., 2006) prevents vessel denudation and formation of microparticles that may contribute to thrombosis (Durand et al., 2004). It has been shown that thrombogenic membrane microparticles that may originate from apoptotic endothelial cells are increased in the plasma of patients with acute coronary syndrome (ACS) (Mallat et al., 2000). Infusion of rHDL in volunteers that received low levels of endotoxin limited the prothrombotic and procoagulant effect of endotoxin (Pajkrt et al., 1997). Furthermore infusion of apoA-I_{MILANO} in a rat model of acute arterial thrombosis increased the time of thrombus formation and decreased the weight of the thrombus (Li et al., 1999). HDL may affect thrombosis via a variety of mechanisms: Early studies showed that HDL causes increased synthesis of prostacyclin in cultured endothelial cells (Fleisher et al., 1983; Tamagaki et al., 1996). Prostacyclin in combination with NO promote smooth muscle cells relaxation, inhibit platelet activation and local smooth muscle cell proliferation (Vane and Botting, 1995). It has been reported that HDL₃ induced expression of cyclooxygenase-2 (Cox-2) by smooth muscle cells and promoted release of prostacyclin (PGI₂) via a signalling pathway that involves p38MAP kinase and c-Jun N terminal kinase

(JNK-1) (Escudero et al., 2003; Vinals et al., 1997). PGI₂ synthesis was enhanced by HMGCoA reductase inhibitors (Martinez-Gonzalez et al., 2004). It has been shown that there is a positive correlation between plasma HDL levels and anticoagulant response to activated protein C (APC)/protein S in vitro (Griffin et al., 1999) and negative correlation with the plasma thrombin activation markers such as prothrombin fragments F1.2 and D-dimer (MacCallum et al., 2000). APC inactivates, by proteolysis, factors Va and VIIIa in plasma and thus it can downregulate thrombin formation. Administration of HDL to cholesterol-fed rabbits also increased endothelial cell thrombomodulin levels, promoted generation of APC and inhibited formation of thrombin (Nicholls et al., 2005a). Glucosylceramide and glycosphingolipids which are present in HDL are lipid cofactors for the anticoagulant activity of APC and in a significant number of patients with venous thrombosis the levels of glucosylceramides are low (Deguchi et al., 2002; Deguchi et al., 2001). Shpingosine, another molecule present in HDL, has been shown to inhibit prothrombin activation on platelets' surface by disrupting procoagulant interactions between factors Xa and Va (Deguchi et al., 2004). HDL also downregulated expression of plasminogen activator inhibitor-1 (PAI-1) and upregulated tissue plasminogen activator (t-PA) in endothelial cell cultures (Eren et al., 2002). Transgenic mice expressing the human PAI-1 developed age-dependent coronary arterial thrombosis (Eren et al., 2002). In contrast oxidized HDL₃ induced the expression of PAI-1 in endothelial cells through signalling mechanisms that involve activation of ERK1/2 and p38MAPK and mRNA stabilization (Norata et al., 2004).

5.6 Effects of HDL on diabetes mellitus

In vivo and in vitro studies have provided evidence that HDL may have beneficial effects on glucose metabolism (Koseki et al., 2009; Rutti et al., 2009). Ex vivo studies showed that HDL and delipidated apoA-I or S1P decreased IL-1 β and glucose-mediated apoptosis and thus increased the survival of human and murine islets. HDL treatment down-regulated the expression of iNOS and its downstream target Fas which is pro-apoptotic and up-regulated the expression of FLICE-like inhibitory protein (FLIP) which is anti-apoptotic (Rutti et al., 2009). HDL also reversed the toxic effects of oxidized LDL on beta cells that are associated with apoptosis and cJNK mediated transcriptional repression of the insulin gene caused cJNK mediated (Abderrahmani et al., 2007).

Oral glucose tolerance test in a limited number of patients with Tangier disease (that lack or have dysfunctional ABCA1) showed that they had glucose intolerance as compared to controls (Koseki et al., 2009), thus implicating ABCA1, apoA-I and HDL in glucose metabolism. Cell culture studies using primary pancreatic islets cells and a pancreatic β -cell line (Min6), showed that lipid free apoA-I or apoA-II or reconstituted HDL increased insulin secretion up to 5-fold in a Ca²⁺ dependant manner (Fryirs et al., 2010). The free apolipoproteins also increased insulin mRNA levels. HDL mediated insulin secretion has also been observed in cultures of mouse pancreatic β -cells (MIN6N8) (Drew et al., 2009). The increase in insulin secretion mediated by lipid-free apoproteins and rHDL required the functions of ABCA1 and SRBI or ABCG1 respectively. These functions may be different from those involved in cholesterol efflux. For high glucose concentrations enhanced insulin secretion required the action of K_{ATP} channel and glucose catabolism in the pancreatic cell, but this did not occur for low glucose concentrations (Fryirs et al., 2010).

Further insight on the role of ABCA1 in diabetes was obtained by studies in mice with selective deficiency of ABCA1 in the pancreas (ABCA1^{-P/-P}). These mice accumulated

cholesterol in their islets and were characterized by impaired acute phase insulin secretion and glucose intolerance. The ABCA1^{-P/-P} mice exhibited normal insulin sensitivity indicating normal response of the peripheral tissues to insulin. The impairment in insulin secretion was verified in cell culture experiments using islets isolated from the ABCA1^{-P/-P} mice. In contrast, whole ABCA1 deficient mice had normal glucose tolerance and displayed only small impairment in the islet function and did not accumulate significant amount of cholesterol in the islets (Brunham et al., 2007). Pancreatic islets isolated from apoE deficient mice had increased cholesterol content and reduced insulin secretion as compared to islets obtained from WT mice. The reduced insulin secretion in the pancreatic islets or cultures of β -cells could be restored by depletion of the cellular cholesterol using mevastatin or methyl- β -cyclodextrin (M β CD) (Hao et al., 2007). Experiments in cell lines of pancreatic β -cell origin indicated that cholesterol loading or cholesterol depletion affect the activity of glucokinase (GK) which is known to regulate insulin secretion (Rizzo and Piston, 2003). The experiments showed that under normal cholesterol levels GK is associated with a dimeric form of nNOS on insulin containing granules in the cytoplasm and is inactive (Rizzo and Piston, 2003). Increase in plasma cholesterol enhanced dimerization of nNOS and its association with GK whereas reduction in the cholesterol levels or increase in the extracellular glucose levels promoted monomerization of nNOS and release of active GK in the cytoplasm (Hao et al., 2007). The role of the increase in the cholesterol content of β -cells in insulin secretion was tested in transgenic mice expressing SREBP-2 in β -cells under the control of insulin promoter. These mice had normal plasma cholesterol levels but developed severe diabetes characterized by 5-fold increase in gluco-hemoglobin and defects in glucose and potassium-stimulated insulin secretion and were characterized by glucose intolerance. The islets were fewer, smaller and deformed and had increased levels of total and esterified cholesterol (Ishikawa et al., 2008). It was proposed that the loss of β -cell mass could be related to the down regulation of genes such as PDX-1 and BETA2 that are involved in β -cell differentiation.

A recent comprehensive study has measured the properties of HDL isolated from patients with type 2 diabetes mellitus and their functions on endothelial cells in vitro and in vivo. HDL isolated from patients with low HDL and type 2 diabetes mellitus contained increased levels of lipid peroxides and increased myeloperoxidase activity. In endothelial cell cultures diabetic HDL had reduced production of NO and increased NADPH oxidase activity that resulted in increased oxidant stress. Diabetic HDL had diminished endothelium dependent relaxation of aortic rings and endothelial progenitor cells obtained from diabetic subjects had diminished capacity to promote reendothelialization in vivo. A remarkable finding in this study was that extended release niacin treatment of the diabetic patients restored the properties and functions of HDL. The HDL obtained after treatment had normal levels of peroxides and normal myeloperoxidase (MPO) activity. Studies with endothelial cultures showed that following treatment of the diabetic patients their HDL could induce normal NO production and NADPH oxidase activity and could promote normal relaxation of aortic rings. Endothelial progenitor cells obtained from diabetic patients following niacin treatment had normal ability to promote reendothelialization in vivo (Sorrentino et al., 2010). In another study intravenous infusion of rHDL (80 mg/kg over 4 hours) in type 2 diabetic human subjects decreased plasma glucose level, increased plasma insulin level and increased β -cell functions as compared to patients receiving placebo (Drew et al., 2009). HDL and apoA-I increased glucose uptake of primary human skeletal muscle cultures established from patients with type 2 diabetes mellitus. HDL induced glucose uptake and fatty acid oxidation and increased AMPK α 2 activity and phosphorylation. These effects

were modulated through a Ca^{2+} dependent pathway. Subsequent *in vitro* and *in vivo* studies showed that rHDL inhibited lipolysis in 3T3-L1 adipocytes partially via activation of AMPK pathway (Drew et al., 2011). Infusion of rHDL also inhibited fasting induced lipolysis and fatty acid oxidation but increased the circulating non essential fatty acids possibly due to the action of phospholipase on the rHDL phospholipids (Drew et al., 2011). The HDL dependent glucose uptake by the skeletal muscle cells was abrogated by inhibition of ABCA1 with a blocking antibody suggesting that ABCA1 functions not related to cholesterol efflux, may contribute to the increased glucose uptake and β -oxidation by skeletal muscle cells obtained from patients with type 2 diabetic mellitus (Drew et al., 2011). The effect of apoA-I on glucose metabolism was also studied in C2C12 myocytes and apoA-I deficient mice. Consistent with the studies with primary human skeletal muscle cultures, apoA-I stimulated AMPK and acetyl-CoA carboxylase (ACC) phosphorylation and glucose uptake and endocytosis into C2C12 cells. The apoA-I deficient mice had increased fat content decreased glucose tolerance and increased expression of gluconeogenic enzymes in the liver and decreased AMPK-dependent phosphorylation in skeletal muscle and the liver (Han et al., 2007).

5.7 Role of apoA-I and HDL in atheroprotection

Atherosclerosis is associated with lipid and lipoprotein abnormalities (Zannis et al., 2004b). Low HDL levels (Gordon et al., 1989) and decreased concentration of the largest size HDL subpopulations (Asztalos et al., 2004) are associated with increased risk of CAD. The anti-atherogenic functions of HDL and apoA-I have been, to a large extent, attributed to the beneficial effects that HDL exerts on cells of the arterial wall as well as their ability to promote efflux from macrophages and other cells of the arterial wall via ABCA1, ABCG1 and SR-BI (Wang et al., 2007). Hepatic overexpression of apoA-I gene in the background of apoE or LDL_r deficient mice reduced the atherosclerosis burden of these mice following an atherogenic diet (Tangirala et al., 1999). These findings demonstrate the importance of apoA-I and HDL for atheroprotection. In contrast, double deficient mice for apoA-I and the LDL_r fed an atherogenic diet developed atherosclerosis and had increased concentration of circulating auto-antibodies, increased population of T, B, dendritic cells and macrophages, as well as increased T cell proliferation and activation. The abnormal phenotype was corrected by adenovirus mediated gene expression of apoA-I (Wilhelm et al., 2010). Similarly apoA-I transgenic rabbits were resistant to diet induced atherosclerosis (Duverger et al., 1996). Two clinical trials showed that intravenous administration of 15 mg/kg of apoA-I_{MILANO}/phospholipid complexes in five weekly doses in patients with acute coronary syndrome resulted in significant regression of atherosclerosis as it was shown by intravascular ultrasound (Nicholls et al., 2006; Nissen et al., 2003). The epidemiological studies (Gordon et al., 1989), combined with studies of experimental animals (Duverger et al., 1996; Tangirala et al., 1999) and clinical intervention studies (Barter et al., 2007; Sorrentino et al., 2010) highlight the importance of increased HDL levels for atheroprotection. However, human subjects have been identified with high HDL levels and CAD (Ansell et al., 2003). In addition, increased HDL levels in humans treated with the CETP inhibitor torcetrapib, increased cardiovascular, and non-cardiovascular deaths (Barter et al., 2007). These findings suggest that high HDL levels are not always synonymous with atheroprotection. The concept that emerges from all the studies is that the most important factor for atheroprotection is the functionality of HDL. Understanding of the structure-function and the cell signaling associated with HDL and apoA-I will provide molecular explanations for their beneficial effects for atherosclerosis and other human diseases and apoA-I.

6. Conclusion

Numerous prospective epidemiological studies have established an inverse correlation between HDL cholesterol levels and the risk for CAD. However, the discovery of human subjects with high HDL cholesterol levels and CAD, combined with clinical intervention studies designed to raise HDL levels and studies of animal models, led to the realization that high levels of HDL cholesterol alone are not sufficient to prevent atherosclerosis. HDL via its protein and/or lipid components participates in numerous interactions with the endothelium, other cells of the vascular wall, as well as with β pancreatic cells, and has a protective effect against atherothrombosis and other diseases. The key proteins that participate in the biogenesis, remodeling and signaling of HDL are of great importance for the functionality of HDL. Mutations in apoA-I, ABCA1 and LCAT affect the biogenesis of HDL and either prevent formation of HDL or generate aberrant HDL subpopulations which may have altered functions. The ability of HDL to inhibit the oxidation of LDL, prevents the induction of pro-inflammatory and pro-apoptotic pathways that are detrimental to the endothelium. HDL interacts directly with the endothelial cells via SR-BI and the ABCG1. These interactions lead to NO release and vasodilatation, promote reendothelialization and suppress expression of adhesion molecules on endothelial cells in response to pro-inflammatory cytokines. As a result of these and other interactions of the sphingolipid components of HDL with S1P receptors, HDL protects from apoptosis and inflammation and promotes endothelial cell growth and migration. Understanding the complexity and the functions of HDL may facilitate in the near future the development of new HDL-based therapies to prevent or treat atherosclerosis and other human diseases.

7. Acknowledgments

This work was supported by National Institutes of Health Grants HL-48739 and HL-68216. A.K. Kateifides and P. Fotakis are students of the graduate program "The Molecular Basis of Human Disease" of the University of Crete, Medical School and were supported by the Greek Ministry of Education, General Secretariat for Research and Technology Grants PENED 03-780 and HRACLEITOS II.

8. References

- Abderrahmani, A., G. Niederhauser, D. Favre et al., 2007, Human high-density lipoprotein particles prevent activation of the JNK pathway induced by human oxidised low-density lipoprotein particles in pancreatic beta cells: *Diabetologia*, v. 50, no. 6, p. 1304-1314.
- Acton, S., A. Rigotti, K. T. Landschulz et al., 1996, Identification of scavenger receptor SR-BI as a high density lipoprotein receptor: *Science*, v. 271, no. 5248, p. 518-520.
- Amar, M. J., R. D. Shamburek, B. Vaisman et al., 2009, Adenoviral expression of human lecithin-cholesterol acyltransferase in nonhuman primates leads to an antiatherogenic lipoprotein phenotype by increasing high-density lipoprotein and lowering low-density lipoprotein: *Metabolism*, v. 58, no. 4, p. 568-575.
- Ansell, B. J., M. Navab, S. Hama et al., 2003, Inflammatory/antiinflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment: *Circulation*, v. 108, no. 22, p. 2751-2756.

- Arai, T., N. Wang, M. Bezouevski et al., 1999, Decreased atherosclerosis in heterozygous low density lipoprotein receptor-deficient mice expressing the scavenger receptor BI transgene: *J.Biol.Chem.*, v. 274, no. 4, p. 2366-2371.
- Assanasen, C., C. Mineo, D. Seetharam et al., 2005, Cholesterol binding, efflux, and a PDZ-interacting domain of scavenger receptor-BI mediate HDL-initiated signaling: *J.Clin.Invest*, v. 115, no. 4, p. 969-977.
- Asztalos, B. F., L. A. Cupples, S. Demissie et al., 2004, High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants of the Framingham Offspring Study: *Arterioscler.Thromb.Vasc.Biol.*, v. 24, no. 11, p. 2181-2187.
- Barter, P. J., H. B. Brewer, Jr., M. J. Chapman et al., 2003, Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis: *Arterioscler.Thromb.Vasc.Biol.*, v. 23, no. 2, p. 160-167.
- Barter, P. J., M. Caulfield, M. Eriksson et al., 2007, Effects of torcetrapib in patients at high risk for coronary events: *N.Engl.J.Med.*, v. 357, no. 21, p. 2109-2122.
- Blair, A., P. W. Shaul, I. S. Yuhanna et al., 1999, Oxidized low density lipoprotein displaces endothelial nitric-oxide synthase (eNOS) from plasmalemmal caveolae and impairs eNOS activation: *J.Biol.Chem.*, v. 274, no. 45, p. 32512-32519.
- Borhani, D. W., D. P. Rogers, J. A. Engler et al., 1997, Crystal structure of truncated human apolipoprotein A-I suggests a lipid-bound conformation: *Proc.Natl.Acad.Sci.U.S.A.*, v. 94, no. 23, p. 12291-12296.
- Braun, A., B. L. Trigatti, M. J. Post et al., 2002, Loss of SR-BI expression leads to the early onset of occlusive atherosclerotic coronary artery disease, spontaneous myocardial infarctions, severe cardiac dysfunction, and premature death in apolipoprotein E-deficient mice: *Circ.Res.*, v. 90, no. 3, p. 270-276.
- Breckenridge, W. C., J. A. Little, P. Alaupovic et al., 1982, Lipoprotein abnormalities associated with a familial deficiency of hepatic lipase: *Atherosclerosis*, v. 45, no. 2, p. 161-179.
- Brodeur, M. R., L. Brissette, L. Falstrault et al., 2008, HDL3 reduces the association and modulates the metabolism of oxidized LDL by osteoblastic cells: a protection against cell death: *J.Cell Biochem.*, v. 105, no. 6, p. 1374-1385.
- Brunham, L. R., J. K. Kruit, T. D. Pape et al., 2007, Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment: *Nat.Med.*, v. 13, no. 3, p. 340-347.
- Brunham, L. R., R. R. Singaraja, and M. R. Hayden, 2006, Variations on a gene: rare and common variants in ABCA1 and their impact on HDL cholesterol levels and atherosclerosis: *Annu.Rev.Nutr.*, v. 26, p. 105-129.
- Brunzell, J. D., and S. S. Deeb, 2001, Familial lipoprotein lipase deficiency, apoC-II deficiency, and hepatic lipase deficiency, in CR Scriver, AL Beaudet, D Valle, and WS Sly eds., *The Metabolic & Molecular Bases of Inherited Disease*: New York, McGraw-Hill, p. 2789-2816.
- Bursill, C. A., M. L. Castro, D. T. Beattie et al., 2010, High-density lipoproteins suppress chemokines and chemokine receptors in vitro and in vivo: *Arterioscler.Thromb.Vasc.Biol.*, v. 30, no. 9, p. 1773-1778.
- Christiansen-Weber, T. A., J. R. Volland, Y. Wu et al., 2000, Functional loss of ABCA1 in mice causes severe placental malformation, aberrant lipid distribution, and kidney glomerulonephritis as well as high-density lipoprotein cholesterol deficiency: *Am.J.Pathol.*, v. 157, no. 3, p. 1017-1029.

- Chroni, A., A. Duka, H. Y. Kan et al., 2005a, Point mutations in apolipoprotein a-I mimic the phenotype observed in patients with classical lecithin:cholesterol acyltransferase deficiency: *Biochemistry*, v. 44, no. 43, p. 14353-14366.
- Chroni, A., H. Y. Kan, K. E. Kypreos et al., 2004, Substitutions of glutamate 110 and 111 in the middle helix 4 of human apolipoprotein A-I (apoA-I) by alanine affect the structure and in vitro functions of apoA-I and induce severe hypertriglyceridemia in apoA-I-deficient mice: *Biochemistry*, v. 43, no. 32, p. 10442-10457.
- Chroni, A., H. Y. Kan, A. Shkodrani et al., 2005b, Deletions of helices 2 and 3 of human apoA-I are associated with severe dyslipidemia following adenovirus-mediated gene transfer in apoA-I-deficient mice: *Biochemistry*, v. 44, no. 10, p. 4108-4117.
- Chroni, A., G. Koukos, A. Duka et al., 2007, The carboxy-terminal region of apoA-I is required for the ABCA1-dependent formation of alpha-HDL but not prebeta-HDL particles in vivo: *Biochemistry*, v. 46, no. 19, p. 5697-5708.
- Chroni, A., T. Liu, I. Gorshkova et al., 2003, The central helices of apoA-I can promote ATP-binding cassette transporter A1 (ABCA1)-mediated lipid efflux. Amino acid residues 220-231 of the wild-type apoA-I are required for lipid efflux in vitro and high density lipoprotein formation in vivo: *J.Biol.Chem.*, v. 278, no. 9, p. 6719-6730.
- Cockerill, G. W., K. A. Rye, J. R. Gamble et al., 1995, High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules: *Arterioscler.Thromb.Vasc.Biol.*, v. 15, no. 11, p. 1987-1994.
- Cybulsky, M. I., and M. A. Gimbrone, Jr., 1991, Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis: *Science*, v. 251, no. 4995, p. 788-791.
- de Souza, J. A., C. Vindis, B. Hansel et al., 2008, Metabolic syndrome features small, apolipoprotein A-I-poor, triglyceride-rich HDL3 particles with defective anti-apoptotic activity: *Atherosclerosis*, v. 197, no. 1, p. 84-94.
- de Souza, J. A., C. Vindis, A. Negre-Salvayre et al., 2010, Small, dense HDL 3 particles attenuate apoptosis in endothelial cells: pivotal role of apolipoprotein A-I: *J.Cell Mol.Med.*, v. 14, no. 3, p. 608-620.
- Deguchi, H., J. A. Fernandez, and J. H. Griffin, 2002, Neutral glycosphingolipid-dependent inactivation of coagulation factor Va by activated protein C and protein S: *Journal of Biological Chemistry*, v. 277, no. 11, p. 8861-8865.
- Deguchi, H., J. A. Fernandez, I. Pabinger et al., 2001, Plasma glucosylceramide deficiency as potential risk factor for venous thrombosis and modulator of anticoagulant protein C pathway: *Blood*, v. 97, no. 7, p. 1907-1914.
- Deguchi, H., N. M. Pecheniuk, D. J. Elias et al., 2005, High-density lipoprotein deficiency and dyslipoproteinemia associated with venous thrombosis in men: *Circulation*, v. 112, no. 6, p. 893-899.
- Deguchi, H., S. Yegneswaran, and J. H. Griffin, 2004, Sphingolipids as bioactive regulators of thrombin generation: *Journal of Biological Chemistry*, v. 279, no. 13, p. 12036-12042.
- Dimmeler, S., K. Breitschopf, J. Haendeler et al., 1999, Dephosphorylation targets Bcl-2 for ubiquitin-dependent degradation: a link between the apoptosome and the proteasome pathway: *J.Exp.Med.*, v. 189, no. 11, p. 1815-1822.
- Dimmeler, S., J. Haendeler, and A. M. Zeiher, 2002, Regulation of endothelial cell apoptosis in atherothrombosis: *Curr.Opin.Lipidol.*, v. 13, no. 5, p. 531-536.

- Doggen, C. J. M., N. L. Smith, R. N. Lemaitre et al., 2004, Serum lipid levels and the risk of venous thrombosis: *Arteriosclerosis Thrombosis and Vascular Biology*, v. 24, no. 10, p. 1970-1975.
- Dole, V. S., J. Matuskova, E. Vasile et al., 2008, Thrombocytopenia and platelet abnormalities in high-density lipoprotein receptor-deficient mice: *Arterioscler.Thromb.Vasc.Biol.*, v. 28, no. 6, p. 1111-1116.
- Drew, B. G., A. L. Carey, A. K. Natoli et al., 2011, Reconstituted high-density lipoprotein infusion modulates fatty acid metabolism in patients with type 2 diabetes mellitus: *Journal of Lipid Research*, v. 52, no. 3, p. 572-581.
- Drew, B. G., S. J. Duffy, M. F. Formosa et al., 2009, High-Density Lipoprotein Modulates Glucose Metabolism in Patients With Type 2 Diabetes Mellitus: *Circulation*, v. 119, no. 15, p. 2103-U134.
- Drew, B. G., N. H. Fidge, G. Gallon-Beaumier et al., 2004, High-density lipoprotein and apolipoprotein AI increase endothelial NO synthase activity by protein association and multisite phosphorylation: *Proc.Natl.Acad.Sci.U.S.A*, v. 101, no. 18, p. 6999-7004.
- Durand, E., A. Scoazec, A. Lafont et al., 2004, In vivo induction of endothelial apoptosis leads to vessel thrombosis and endothelial denudation - A clue to the understanding of the mechanisms of thrombotic plaque erosion: *Circulation*, v. 109, no. 21, p. 2503-2506.
- Duverger, N., H. Kruth, F. Emmanuel et al., 1996, Inhibition of atherosclerosis development in cholesterol-fed human apolipoprotein A-I-transgenic rabbits: *Circulation*, v. 94, no. 4, p. 713-717.
- Eren, M., C. A. Painter, J. B. Atkinson et al., 2002, Age-dependent spontaneous coronary arterial thrombosis in transgenic mice that express a stable form of human plasminogen activator inhibitor-1: *Circulation*, v. 106, no. 4, p. 491-496.
- Escudero, I., J. Martinez-Gonzalez, R. Alonso et al., 2003, Experimental and interventional dietary study in humans on the role of HDL fatty acid composition in PGI(2) release and Cox-2 expression by VSMC: *European Journal of Clinical Investigation*, v. 33, no. 9, p. 779-786.
- Fielding, C. J., V. G. Shore, and P. E. Fielding, 1972, A protein cofactor of lecithin:cholesterol acyltransferase: *Biochem.Biophys.Res.Comm.*, v. 46, no. 4, p. 1493-1498.
- Fleisher, L. N., A. R. Tall, L. D. Witte et al., 1983, Effects of high-density lipoprotein and the apoprotein of high-density lipoprotein on Prostacyclin synthesis by endothelial cells: *Advances in Prostaglandin Thromboxane and Leukotriene Research*, v. 11, p. 475-480.
- Frikke-Schmidt, R., B. G. Nordestgaard, G. B. Jensen et al., 2008, Genetic variation in ABCA1 predicts ischemic heart disease in the general population: *Arterioscler.Thromb.Vasc.Biol.*, v. 28, no. 1, p. 180-186.
- Fryirs, M. A., P. J. Barter, M. Appavoo et al., 2010, Effects of High-Density Lipoproteins on Pancreatic beta-Cell Insulin Secretion: *Arteriosclerosis Thrombosis and Vascular Biology*, v. 30, no. 8, p. 1642-U296.
- Gharavi, N. M., N. A. Baker, K. P. Mouillessaux et al., 2006, Role of endothelial nitric oxide synthase in the regulation of SREBP activation by oxidized phospholipids: *Circ.Res.*, v. 98, no. 6, p. 768-776.
- Gomaschi, M., L. Calabresi, G. Rossoni et al., 2008, Anti-inflammatory and cardioprotective activities of synthetic high-density lipoprotein containing apolipoprotein A-I mimetic peptides: *J.Pharmacol.Exp.Ther.*, v. 324, no. 2, p. 776-783.

- Gong, M., M. Wilson, T. Kelly et al., 2003, HDL-associated estradiol stimulates endothelial NO synthase and vasodilation in an SR-BI-dependent manner: *J.Clin.Invest*, v. 111, no. 10, p. 1579-1587.
- Gordon, D. J., J. L. Probstfield, R. J. Garrison et al., 1989, High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies: *Circulation*, v. 79, no. 1, p. 8-15.
- Grewal, T., D. de, I. M. F. Kirchhoff et al., 2003, High density lipoprotein-induced signaling of the MAPK pathway involves scavenger receptor type BI-mediated activation of Ras: *J.Biol.Chem.*, v. 278, no. 19, p. 16478-16481.
- Griffin, J. H., K. Kojima, C. L. Banka et al., 1999, High-density lipoprotein enhancement of anticoagulant activities of plasma protein S and activated protein C: *Journal of Clinical Investigation*, v. 103, no. 2, p. 219-227.
- Gu, X., K. Kozarsky, and M. Krieger, 2000, Scavenger receptor class B, type I-mediated [3H]cholesterol efflux to high and low density lipoproteins is dependent on lipoprotein binding to the receptor: *J.Biol.Chem.*, v. 275, no. 39, p. 29993-30001.
- Haase, C. L., R. Frikke-Schmidt, B. G. Nordestgaard et al., 2011, Mutation in APOA1 predicts increased risk of ischaemic heart disease and total mortality without low HDL cholesterol levels: *J.Intern.Med.*
- Han, R., R. Lai, Q. Ding et al., 2007, Apolipoprotein A-I stimulates AMP-activated protein kinase and improves glucose metabolism: *Diabetologia*, v. 50, no. 9, p. 1960-1968.
- Hao, M., W. S. Head, S. C. Gunawardana et al., 2007, Direct effect of cholesterol on insulin secretion - A novel mechanism for pancreatic beta-cell dysfunction: *Diabetes*, v. 56, no. 9, p. 2328-2338.
- Holm, T. M., A. Braun, B. L. Trigatti et al., 2002, Failure of red blood cell maturation in mice with defects in the high-density lipoprotein receptor SR-BI: *Blood*, v. 99, no. 5, p. 1817-1824.
- Huszar, D., M. L. Varban, F. Rinninger et al., 2000, Increased LDL cholesterol and atherosclerosis in LDL receptor-deficient mice with attenuated expression of scavenger receptor B1: *Arterioscler.Thromb.Vasc.Biol.*, v. 20, no. 4, p. 1068-1073.
- Ishida, T., S. Choi, R. K. Kundu et al., 2003, Endothelial lipase is a major determinant of HDL level: *J.Clin.Invest*, v. 111, no. 3, p. 347-355.
- Ishikawa, M., Y. Iwasaki, S. Yatoh et al., 2008, Cholesterol accumulation and diabetes in pancreatic beta-cell-specific SREBP-2 transgenic mice: a new model for lipotoxicity: *Journal of Lipid Research*, v. 49, no. 12, p. 2524-2534.
- Ji, Y., N. Wang, R. Ramakrishnan et al., 1999, Hepatic scavenger receptor BI promotes rapid clearance of high density lipoprotein free cholesterol and its transport into bile: *J.Biol.Chem.*, v. 274, no. 47, p. 33398-33402.
- Joyce, C. W., M. J. Amar, G. Lambert et al., 2002, The ATP binding cassette transporter A1 (ABCA1) modulates the development of aortic atherosclerosis in C57BL/6 and apoE-knockout mice: *Proc.Natl.Acad.Sci.U.S.A.*, v. 99, no. 1, p. 407-412.
- Kateifides, A. K., I. N. Gorshkova, A. Duka et al., 2011, Alteration of negatively charged residues in the 89 to 99 domain of apoA-I affects lipid homeostasis and maturation of HDL: *J.Lipid Res.*, v. 52, no. 7, p. 1363-1372.
- Kennedy, M. A., G. C. Barrera, K. Nakamura et al., 2005, ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation: *Cell Metab*, v. 1, no. 2, p. 121-131.

- Kielar, D., W. Dietmaier, T. Langmann et al., 2001, Rapid quantification of human ABCA1 mRNA in various cell types and tissues by real-time reverse transcription-PCR: *Clin.Chem.*, v. 47, no. 12, p. 2089-2097.
- Kimura, T., K. Sato, E. Malchinkhuu et al., 2003, High-density lipoprotein stimulates endothelial cell migration and survival through sphingosine 1-phosphate and its receptors: *Arterioscler.Thromb.Vasc.Biol.*, v. 23, no. 7, p. 1283-1288.
- Kocher, O., A. Yesilaltay, C. Cirovic et al., 2003, Targeted disruption of the PDZK1 gene in mice causes tissue-specific depletion of the HDL Receptor SR-BI and altered lipoprotein metabolism: *J.Biol.Chem.*, v. 278, p. 52820-52825.
- Koseki, M., A. Matsuyama, K. Nakatani et al., 2009, Impaired Insulin Secretion in Four Tangier Disease Patients with ABCA1 Mutations: *Journal of Atherosclerosis and Thrombosis*, v. 16, no. 3, p. 292-296.
- Koukos, G., A. Chroni, A. Duka et al., 2007, LCAT can rescue the abnormal phenotype produced by the natural ApoA-I mutations (Leu141Arg)Pisa and (Leu159Arg)FIN: *Biochemistry*, v. 46, no. 37, p. 10713-10721.
- Krauss, R. M., R. I. Levy, and D. S. Fredrickson, 1974, Selective measurement of two lipase activities in postheparin plasma from normal subjects and patients with hyperlipoproteinemia: *J.Clin.Invest*, v. 54, no. 5, p. 1107-1124.
- Krieger, M., 2001, Scavenger receptor class B type I is a multiligand HDL receptor that influences diverse physiologic systems: *J.Clin.Invest*, v. 108, no. 6, p. 793-797.
- Li, D., B. Yang, and J. L. Mehta, 1998, Ox-LDL induces apoptosis in human coronary artery endothelial cells: role of PKC, PTK, bcl-2, and Fas: *Am.J.Physiol*, v. 275, no. 2 Pt 2, p. H568-H576.
- Li, D. Y., S. Weng, B. C. Yang et al., 1999, Inhibition of arterial thrombus formation by apoA1 Milano: *Arteriosclerosis Thrombosis and Vascular Biology*, v. 19, no. 2, p. 378-383.
- Li, X. A., L. Guo, J. L. Dressman et al., 2005, A novel ligand-independent apoptotic pathway induced by SR-BI and suppressed by eNOS and HDL: *J.Biol.Chem.*, v. 280, p. 19087-19096.
- Li, X. A., W. B. Titlow, B. A. Jackson et al., 2002, High density lipoprotein binding to scavenger receptor, Class B, type I activates endothelial nitric-oxide synthase in a ceramide-dependent manner: *J.Biol.Chem.*, v. 277, no. 13, p. 11058-11063.
- Li, X. P., S. P. Zhao, X. Y. Zhang et al., 2000, Protective effect of high density lipoprotein on endothelium-dependent vasodilatation: *Int.J.Cardiol.*, v. 73, no. 3, p. 231-236.
- Liadaki, K. N., T. Liu, S. Xu et al., 2000, Binding of high density lipoprotein (HDL) and discoidal reconstituted HDL to the HDL receptor scavenger receptor class B type I. Effect of lipid association and APOA-I mutations on receptor binding: *J.Biol.Chem.*, v. 275, no. 28, p. 21262-21271.
- Lusa, S., M. Jauhiainen, J. Metso et al., 1996, The mechanism of human plasma phospholipid transfer protein-induced enlargement of high-density lipoprotein particles: evidence for particle fusion: *Biochem.J.*, v. 313 (Pt 1), p. 275-282.
- MacCallum, P. K., J. A. Cooper, J. Martin et al., 2000, Haemostatic and lipid determinants of prothrombin fragment F1.2 and D-dimer in plasma: *Thrombosis and Haemostasis*, v. 83, no. 3, p. 421-426.
- Mallat, Z., H. Benamer, B. Hugel et al., 2000, Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes: *Circulation*, v. 101, no. 8, p. 841-843.

- Mardones, P., V. Quinones, L. Amigo et al., 2001, Hepatic cholesterol and bile acid metabolism and intestinal cholesterol absorption in scavenger receptor class B type I-deficient mice: *J.Lipid Res.*, v. 42, no. 2, p. 170-180.
- Martinez-Gonzalez, J., I. Escudero, and L. Badimon, 2004, Simvastatin potentiates PGI(2) release induced by HDL in human VSMC: effect on Cox-2 up-regulation and MAPK signalling pathways activated by HDL: *Atherosclerosis*, v. 174, no. 2, p. 305-313.
- Matsunaga, T., Y. Hiasa, H. Yanagi et al., 1991, Apolipoprotein A-I deficiency due to a codon 84 nonsense mutation of the apolipoprotein A-I gene: *Proc.Natl.Acad.Sci.U.S.A.*, v. 88, no. 7, p. 2793-2797.
- McNeish, J., R. J. Aiello, D. Guyot et al., 2000, High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1: *Proc.Natl.Acad.Sci.U.S.A.*, v. 97, no. 8, p. 4245-4250.
- Mineo, C., H. Deguchi, J. H. Griffin et al., 2006, Endothelial and antithrombotic actions of HDL: *Circ.Res.*, v. 98, no. 11, p. 1352-1364.
- Mineo, C., I. S. Yuhanna, M. J. Quon et al., 2003, High density lipoprotein-induced endothelial nitric-oxide synthase activation is mediated by Akt and MAP kinases: *J.Biol.Chem.*, v. 278, no. 11, p. 9142-9149.
- Miura, S., M. Fujino, Y. Matsuo et al., 2003, High density lipoprotein-induced angiogenesis requires the activation of Ras/MAP kinase in human coronary artery endothelial cells: *Arterioscler.Thromb.Vasc.Biol.*, v. 23, no. 5, p. 802-808.
- Murphy, A. J., K. J. Woollard, A. Hoang et al., 2008, High-density lipoprotein reduces the human monocyte inflammatory response: *Arterioscler.Thromb.Vasc.Biol.*, v. 28, no. 11, p. 2071-2077.
- Murugesan, G., G. Sa, and P. L. Fox, 1994, High-density lipoprotein stimulates endothelial cell movement by a mechanism distinct from basic fibroblast growth factor: *Circ.Res.*, v. 74, no. 6, p. 1149-1156.
- Mythreye, K., L. L. Satterwhite, W. S. Davidson et al., 2008, ApoA-I induced CD31 in bone marrow-derived vascular progenitor cells increases adhesion: implications for vascular repair: *Biochim.Biophys.Acta*, v. 1781, no. 11-12, p. 703-709.
- Nakamura, K., M. A. Kennedy, A. Baldan et al., 2004, Expression and regulation of multiple murine ATP-binding cassette transporter G1 mRNAs/isoforms that stimulate cellular cholesterol efflux to high density lipoprotein: *J.Biol.Chem.*, v. 279, no. 44, p. 45980-45989.
- Navab, M., S. Y. Hama, G. M. Anantharamaiah et al., 2000a, Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3: *J.Lipid Res.*, v. 41, no. 9, p. 1495-1508.
- Navab, M., S. Y. Hama, C. J. Cooke et al., 2000b, Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1: *J.Lipid Res.*, v. 41, no. 9, p. 1481-1494.
- Nicholls, S. J., B. Cutri, S. G. Worthley et al., 2005a, Impact of short-term administration of high-density lipoproteins and atorvastatin on atherosclerosis in rabbits: *Arteriosclerosis Thrombosis and Vascular Biology*, v. 25, no. 11, p. 2416-2421.
- Nicholls, S. J., G. J. Dusting, B. Cutri et al., 2005b, Reconstituted high-density lipoproteins inhibit the acute pro-oxidant and proinflammatory vascular changes induced by a periarterial collar in normocholesterolemic rabbits: *Circulation*, v. 111, no. 12, p. 1543-1550.

- Nicholls, S. J., E. M. Tuzcu, I. Sipahi et al., 2006, Relationship between atheroma regression and change in lumen size after infusion of apolipoprotein A-I Milano: *J.Am.Coll.Cardiol.*, v. 47, no. 5, p. 992-997.
- Nissen, S. E., T. Tsunoda, E. M. Tuzcu et al., 2003, Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial: *JAMA*, v. 290, no. 17, p. 2292-2300.
- Nobecourt, E., F. Tabet, G. Lambert et al., 2010, Nonenzymatic glycation impairs the antiinflammatory properties of apolipoprotein A-I: *Arterioscler.Thromb.Vasc.Biol.*, v. 30, no. 4, p. 766-772.
- Nofer, J. R., B. Levkau, I. Wolinska et al., 2001, Suppression of endothelial cell apoptosis by high density lipoproteins (HDL) and HDL-associated lysosphingolipids: *J.Biol.Chem.*, v. 276, no. 37, p. 34480-34485.
- Nofer, J. R., G. M. van der, M. Tolle et al., 2004, HDL induces NO-dependent vasorelaxation via the lysophospholipid receptor S1P3: *J.Clin.Invest*, v. 113, no. 4, p. 569-581.
- Nolte, R. T., and D. Atkinson, 1992, Conformational analysis of apolipoprotein A-I and E-3 based on primary sequence and circular dichroism: *Biophys.J.*, v. 63, no. 5, p. 1221-1239.
- Noor, R., U. Shuaib, C. X. Wang et al., 2007, High-density lipoprotein cholesterol regulates endothelial progenitor cells by increasing eNOS and preventing apoptosis: *Atherosclerosis*, v. 192, no. 1, p. 92-99.
- Norata, G. D., C. Banfi, A. Pirillo et al., 2004, Oxidised-HDL3 induces the expression of PAI-1 in human endothelial cells. Role of p38MAPK activation and mRNA stabilization: *British Journal of Haematology*, v. 127, no. 1, p. 97-104.
- Norata, G. D., E. Callegari, M. Marchesi et al., 2005, High-density lipoproteins induce transforming growth factor-beta2 expression in endothelial cells: *Circulation*, v. 111, no. 21, p. 2805-2811.
- Okajima, F., K. Sato, and T. Kimura, 2009, Anti-atherogenic actions of high-density lipoprotein through sphingosine 1-phosphate receptors and scavenger receptor class B type I: *Endocr.J.*, v. 56, no. 3, p. 317-334.
- Okura, H., S. Yamashita, T. Ohama et al., 2010, HDL/Apolipoprotein A-I Binds to Macrophage-Derived Progranulin and Suppresses its Conversion into Proinflammatory Granulins: *Journal of Atherosclerosis and Thrombosis*, v. 17, no. 6, p. 568-577.
- Ou, Z., J. Ou, A. W. Ackerman et al., 2003, L-4F, an apolipoprotein A-1 mimetic, restores nitric oxide and superoxide anion balance in low-density lipoprotein-treated endothelial cells: *Circulation*, v. 107, no. 11, p. 1520-1524.
- Out, R., M. Hoekstra, J. A. Spijkers et al., 2004, Scavenger receptor class B type I is solely responsible for the selective uptake of cholesteryl esters from HDL by the liver and the adrenals in mice: *J.Lipid Res.*, v. 45, no. 11, p. 2088-2095.
- Out, R., W. Jessup, W. Le Goff et al., 2008, Coexistence of foam cells and hypocholesterolemia in mice lacking the ABC transporters A1 and G1: *Circ.Res.*, v. 102, no. 1, p. 113-120.
- Pajkrt, D., P. G. Lerch, T. vanderPoll et al., 1997, Differential effects of reconstituted high-density lipoprotein on coagulation, fibrinolysis and platelet activation during human endotoxemia: *Thrombosis and Haemostasis*, v. 77, no. 2, p. 303-307.
- Parker, T. S., D. M. Levine, J. C. C. Chang et al., 1995, Reconstituted High-Density-Lipoprotein Neutralizes Gram-Negative Bacterial Lipopolysaccharides in Human Whole-Blood: *Infection and Immunity*, v. 63, no. 1, p. 253-258.

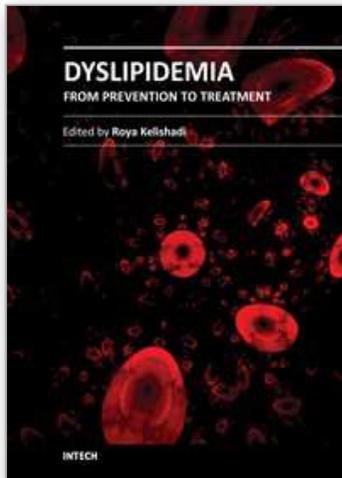
- Patel, S., B. G. Drew, S. Nakhla et al., 2009, Reconstituted high-density lipoprotein increases plasma high-density lipoprotein anti-inflammatory properties and cholesterol efflux capacity in patients with type 2 diabetes: *J.Am.Coll.Cardiol.*, v. 53, no. 11, p. 962-971.
- Peters, W., and I. F. Charo, 2001, Involvement of chemokine receptor 2 and its ligand, monocyte chemoattractant protein-1, in the development of atherosclerosis: lessons from knockout mice: *Curr Opin Lipidol.*, v. 12, no. 2, p. 175-180.
- Radojkovic, C., A. Genoux, V. Pons et al., 2009, Stimulation of Cell Surface F-1-ATPase Activity by Apolipoprotein A-I Inhibits Endothelial Cell Apoptosis and Promotes Proliferation: *Arteriosclerosis Thrombosis and Vascular Biology*, v. 29, no. 7, p. 1125-U214.
- Ramet, M. E., M. Ramet, Q. Lu et al., 2003, High-density lipoprotein increases the abundance of eNOS protein in human vascular endothelial cells by increasing its half-life: *Journal of the American College of Cardiology*, v. 41, no. 12, p. 2288-2297.
- Remaley, A. T., J. A. Stonik, S. J. Demosky et al., 2001, Apolipoprotein specificity for lipid efflux by the human ABCA1 transporter: *Biochem.Biophys.Res.Commun.*, v. 280, no. 3, p. 818-823.
- Rigotti, A., B. L. Trigatti, M. Penman et al., 1997, A targeted mutation in the murine gene encoding the high density lipoprotein (HDL) receptor scavenger receptor class B type I reveals its key role in HDL metabolism: *Proc.Natl.Acad.Sci.U.S.A.*, v. 94, no. 23, p. 12610-12615.
- Rizzo, M. A., and D. W. Piston, 2003, Regulation of beta cell glucokinase by S-nitrosylation and association with nitric oxide synthase: *Journal of Cell Biology*, v. 161, no. 2, p. 243-248.
- Rutti, S., J. A. Ehses, R. A. Sibling et al., 2009, Low- and high-density lipoproteins modulate function, apoptosis, and proliferation of primary human and murine pancreatic beta-cells: *Endocrinology*, v. 150, no. 10, p. 4521-4530.
- Santamarina-Fojo, S., J. M. Hoeg, G. Assmann, and H. B. Brewer, Jr., 2001, Lecithin cholesterol acyltransferase deficiency and fish eye disease, in CR Scriver, AL Beaudet, WS Sly, and D Valle eds., *The Metabolic & Molecular Bases of Inherited Disease*: New York, McGraw-Hill, p. 2817-2834.
- Savary, S., F. Denizot, M. Luciani et al., 1996, Molecular cloning of a mammalian ABC transporter homologous to Drosophila white gene: *Mamm.Genome*, v. 7, no. 9, p. 673-676.
- Seetharam, D., C. Mineo, A. K. Gormley et al., 2006, High-density lipoprotein promotes endothelial cell migration and reendothelialization via scavenger receptor-B type I: *Circulation Research*, v. 98, no. 1, p. 63-72.
- Silver, D. L., N. Wang, X. Xiao et al., 2001, High density lipoprotein (HDL) particle uptake mediated by scavenger receptor class B type 1 results in selective sorting of HDL cholesterol from protein and polarized cholesterol secretion: *J.Biol.Chem.*, v. 276, no. 27, p. 25287-25293.
- Singaraja, R. R., L. R. Brunham, H. Visscher et al., 2003, Efflux and atherosclerosis: the clinical and biochemical impact of variations in the ABCA1 gene: *Arterioscler.Thromb.Vasc.Biol.*, v. 23, no. 8, p. 1322-1332.
- Singh, I. P., A. K. Chopra, D. H. Coppenhaver et al., 1999, Lipoproteins account for part of the broad non-specific antiviral activity of human serum: *Antiviral Research*, v. 42, no. 3, p. 211-218.

- Sorci-Thomas, M. G., and M. J. Thomas, 2002, The effects of altered apolipoprotein A-I structure on plasma HDL concentration: *Trends Cardiovasc.Med.*, v. 12, no. 3, p. 121-128.
- Sorrentino, S. A., C. Besler, L. Rohrer et al., 2010, Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy: *Circulation*, v. 121, no. 1, p. 110-122.
- Stangl, H., M. Hyatt, and H. H. Hobbs, 1999, Transport of lipids from high and low density lipoproteins via scavenger receptor-BI: *J.Biol.Chem.*, v. 274, no. 46, p. 32692-32698.
- Strawn, W. B., and C. M. Ferrario, 2002, Mechanisms linking angiotensin II and atherogenesis: *Curr.Opin.Lipidol.*, v. 13, no. 5, p. 505-512.
- Suc, I., I. Escargueil-Blanc, M. Trolly et al., 1997, HDL and ApoA prevent cell death of endothelial cells induced by oxidized LDL: *Arterioscler.Thromb.Vasc.Biol.*, v. 17, no. 10, p. 2158-2166.
- Sugano, M., K. Tsuchida, and N. Makino, 2000, High-density lipoproteins protect endothelial cells from tumor necrosis factor-alpha-induced apoptosis: *Biochem.Biophys.Res.Commun.*, v. 272, no. 3, p. 872-876.
- Tabet, F., A. T. Remaley, A. I. Segaliny et al., 2010, The 5A apolipoprotein A-I mimetic peptide displays antiinflammatory and antioxidant properties in vivo and in vitro: *Arterioscler.Thromb.Vasc.Biol.*, v. 30, no. 2, p. 246-252.
- Tamagaki, T., S. Sawada, H. Imamura et al., 1996, Effects of high-density lipoproteins on intracellular pH and proliferation of human vascular endothelial cells: *Atherosclerosis*, v. 123, no. 1-2, p. 73-82.
- Tangirala, R. K., K. Tsukamoto, S. H. Chun et al., 1999, Regression of atherosclerosis induced by liver-directed gene transfer of apolipoprotein A-I in mice: *Circulation*, v. 100, no. 17, p. 1816-1822.
- Terasaka, N., M. Westerterp, J. Koetsveld et al., 2010, ATP-binding cassette transporter G1 and high-density lipoprotein promote endothelial NO synthesis through a decrease in the interaction of caveolin-1 and endothelial NO synthase: *Arterioscler.Thromb.Vasc.Biol.*, v. 30, no. 11, p. 2219-2225.
- Thuahnai, S. T., S. Lund-Katz, D. L. Williams et al., 2001, Scavenger receptor class B, type I-mediated uptake of various lipids into cells. Influence of the nature of the donor particle interaction with the receptor: *J.Biol.Chem.*, v. 276, no. 47, p. 43801-43808.
- Tolle, M., A. Pawlak, M. Schuchardt et al., 2008, HDL-associated lysosphingolipids inhibit NAD(P)H oxidase-dependent monocyte chemoattractant protein-1 production: *Arteriosclerosis Thrombosis and Vascular Biology*, v. 28, no. 8, p. 1542-1548.
- Trigatti, B., H. Rayburn, M. Vinals et al., 1999, Influence of the high density lipoprotein receptor SR-BI on reproductive and cardiovascular pathophysiology: *Proc.Natl.Acad.Sci.U.S.A.*, v. 96, no. 16, p. 9322-9327.
- Ueda, Y., L. Royer, E. Gong et al., 1999, Lower plasma levels and accelerated clearance of high density lipoprotein (HDL) and non-HDL cholesterol in scavenger receptor class B type I transgenic mice: *J.Biol.Chem.*, v. 274, no. 11, p. 7165-7171.
- Uittenbogaard, A., P. W. Shaul, I. S. Yuhanna et al., 2000, High density lipoprotein prevents oxidized low density lipoprotein-induced inhibition of endothelial nitric-oxide synthase localization and activation in caveolae: *Journal of Biological Chemistry*, v. 275, no. 15, p. 11278-11283.

- Van Eck, M., I. S. Bos, W. E. Kaminski et al., 2002, Leukocyte ABCA1 controls susceptibility to atherosclerosis and macrophage recruitment into tissues: *Proc.Natl.Acad.Sci. U.S.A*, v. 99, no. 9, p. 6298-6303.
- Van Eck, M., R. R. Singaraja, D. Ye et al., 2006, Macrophage ATP-binding cassette transporter A1 overexpression inhibits atherosclerotic lesion progression in low-density lipoprotein receptor knockout mice: *Arterioscler.Thromb.Vasc.Biol.*, v. 26, no. 4, p. 929-934.
- Vane, J. R., and R. M. Botting, 1995, Pharmacodynamic Profile of Prostacyclin: *American Journal of Cardiology*, v. 75, no. 3, p. A3-A10.
- Vanhollebeke, B., and E. Pays, 2010, The trypanolytic factor of human serum: many ways to enter the parasite, a single way to kill: *Molecular Microbiology*, v. 76, no. 4, p. 806-814.
- Vantourout, P., C. Radojkovic, L. Lichtenstein et al., 2010, Ecto-F-ATPase: a moonlighting protein complex and an unexpected apoA-I receptor: *World J.Gastroenterol.*, v. 16, no. 47, p. 5925-5935.
- Vaughan, A. M., and J. F. Oram, 2005, ABCG1 redistributes cell cholesterol to domains removable by HDL but not by lipid-depleted apolipoproteins: *J.Biol.Chem.*, v. 280, p. 30150-30157.
- Vergeer, M., S. J. A. Korpelaar, R. Franssen et al., 2011, Genetic Variant of the Scavenger Receptor BI in Humans: *New England Journal of Medicine*, v. 364, no. 2, p. 136-145.
- Vinals, M., J. Martinez-Gonzalez, J. J. Badimon et al., 1997, HDL-induced prostacyclin release in smooth muscle cells is dependent on cyclooxygenase-2 (Cox-2): *Arteriosclerosis Thrombosis and Vascular Biology*, v. 17, no. 12, p. 3481-3488.
- Wang, N., D. Lan, W. Chen et al., 2004, ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins: *Proc.Natl.Acad.Sci. U.S.A*, v. 101, no. 26, p. 9774-9779.
- Wang, N., D. L. Silver, P. Costet et al., 2000, Specific binding of ApoA-I, enhanced cholesterol efflux, and altered plasma membrane morphology in cells expressing ABC1: *J.Biol.Chem.*, v. 275, no. 42, p. 33053-33058.
- Wang, X., H. L. Collins, M. Ranalletta et al., 2007, Macrophage ABCA1 and ABCG1, but not SR-BI, promote macrophage reverse cholesterol transport in vivo: *J.Clin.Invest*, v. 117, no. 8, p. 2216-2224.
- Welch, G. N., and J. Loscalzo, 1998, Homocysteine and atherothrombosis: *N.Engl.J.Med.*, v. 338, no. 15, p. 1042-1050.
- Werner, N., S. Junk, U. Laufs et al., 2003, Intravenous transfusion of endothelial progenitor cells reduces neointima formation after vascular injury: *Circ.Res.*, v. 93, p. e17-e24.
- Wilhelm, A. J., M. Zabalawi, J. S. Owen et al., 2010, Apolipoprotein A-I modulates regulatory T cells in autoimmune LDLr^{-/-}, ApoA-I^{-/-} mice: *J.Biol.Chem.*, v. 285, no. 46, p. 36158-36169.
- Williamson, R., D. Lee, J. Hagan et al., 1992, Marked reduction of high density lipoprotein cholesterol in mice genetically modified to lack apolipoprotein A-I: *Proc.Natl.Acad.Sci.U.S.A*, v. 89, no. 15, p. 7134-7138.
- Wu, Z., V. Gogonea, X. Lee et al., 2011, The low resolution structure of ApoA1 in spherical high density lipoprotein revealed by small angle neutron scattering: *J.Biol.Chem.*
- Yao, Y., E. S. Shao, M. Jumabay et al., 2008, High-density lipoproteins affect endothelial BMP-signaling by modulating expression of the activin-like kinase receptor 1 and 2: *Arterioscler.Thromb.Vasc.Biol.*, v. 28, no. 12, p. 2266-2274.

- Yates, M., A. Kolmakova, Y. Zhao et al., 2011, Clinical impact of scavenger receptor class B type I gene polymorphisms on human female fertility: *Hum.Reprod.*
- Yeh, M., A. L. Cole, J. Choi et al., 2004, Role for sterol regulatory element-binding protein in activation of endothelial cells by phospholipid oxidation products: *Circ.Res.*, v. 95, no. 8, p. 780-788.
- Yesilaltay, A., M. G. Morales, L. Amigo et al., 2006, Effects of hepatic expression of the high-density lipoprotein receptor SR-BI on lipoprotein metabolism and female fertility: *Endocrinology*, v. 147, no. 4, p. 1577-1588.
- Yuhanna, I. S., Y. Zhu, B. E. Cox et al., 2001, High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase: *Nat.Med.*, v. 7, no. 7, p. 853-857.
- Yvan-Charvet, L., M. Ranalletta, N. Wang et al., 2007, Combined deficiency of ABCA1 and ABCG1 promotes foam cell accumulation and accelerates atherosclerosis in mice: *J.Clin.Invest*, v. 117, no. 12, p. 3900-3908.
- Zannis, V. I., A. Chroni, and M. Krieger, 2006a, Role of apoA-I, ABCA1, LCAT, and SR-BI in the biogenesis of HDL: *J.Mol.Med.*, v. 84, no. 4, p. 276-294.
- Zannis, V. I., A. Chroni, K. E. Kypreos et al., 2004a, Probing the pathways of chylomicron and HDL metabolism using adenovirus-mediated gene transfer: *Curr Opin Lipidol.*, v. 15, no. 2, p. 151-166.
- Zannis, V. I., D. Kardassis, and E. E. Zanni, 1993, Genetic mutations affecting human lipoproteins, their receptors, and their enzymes: *Adv.Hum.Genet.*, v. 21, p. 145-319.
- Zannis, V. I., K. E. Kypreos, A. Chroni, D. Kardassis, and E. E. Zanni, 2004b, Lipoproteins and atherogenesis, in J Loscalzo ed., *Molecular Mechanisms of Atherosclerosis*: New York, NY, Taylor & Francis, p. 111-174.
- Zannis, V. I., E. E. Zanni, A. Papapanagiotou, D. Kardassis, and A. Chroni, 2006b, ApoA-I functions and synthesis of HDL: Insights from mouse models of human HDL metabolism, *High-Density Lipoproteins. From Basic Biology to Clinical Aspects*: Weinheim, Wiley-VCH, p. 237-265.
- Zeihner, A. M., V. Schachlinger, S. H. Hohnloser et al., 1994, Coronary atherosclerotic wall thickening and vascular reactivity in humans. Elevated high-density lipoprotein levels ameliorate abnormal vasoconstriction in early atherosclerosis: *Circulation*, v. 89, no. 6, p. 2525-2532.

IntechOpen



Dyslipidemia - From Prevention to Treatment

Edited by Prof. Roya Kelishadi

ISBN 978-953-307-904-2

Hard cover, 468 pages

Publisher InTech

Published online 03, February, 2012

Published in print edition February, 2012

Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Vassilis Zannis, Andreas Kateifides, Panagiotis Fotakis, Eleni Zanni and Dimitris Kardassis (2012). Pleiotropic Functions of HDL Lead to Protection from Atherosclerosis and Other Diseases, *Dyslipidemia - From Prevention to Treatment*, Prof. Roya Kelishadi (Ed.), ISBN: 978-953-307-904-2, InTech, Available from: <http://www.intechopen.com/books/dyslipidemia-from-prevention-to-treatment/pleiotropic-functions-of-hdl-lead-to-protection-from-atherosclerosis-and-other-diseases>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen