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High-Density Lipoprotein Regulation of Mitochondrial function

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Abstract

Lipoproteins play a key role in regulating plasma and tissue levels of cholesterol. Apolipoprotein B (apoB)-containing lipoproteins, including chylomicrons, very-low density lipoprotein (VLDL) and low-density lipoprotein (LDL), serve as carriers of triglycerides and cholesterol and deliver these metabolites to peripheral tissues. In contrast, high-density lipoprotein (HDL) mediates Reverse Cholesterol Transport (RCT), a process by which excess cholesterol is removed from the periphery and taken up by hepatocytes where it is metabolized and excreted. Anti-atherogenic properties of HDL have been largely ascribed to apoA-I, the major protein component of the lipoprotein particle. The inflammatory response associated with atherosclerosis and ischemia-reperfusion (I-R) injury has been linked to the development of mitochondrial dysfunction. Under these conditions, an increase in reactive oxygen species (ROS) formation induces damage to mitochondrial structural elements, leading to a reduction in ATP synthesis and initiation of the apoptotic program. Recent studies suggest that HDL-associated apoA-I and lysosphingolipids attenuate mitochondrial injury by multiple mechanisms, including the suppression of ROS formation and induction of autophagy. Other apolipoproteins, however, present in lower abundance in HDL particles may exert opposing effects on mitochondrial function. This chapter examines the role of HDL-associated apolipoproteins and lipids in the regulation of mitochondrial function and bioenergetics.

Keywords

Mitochondria; apolipoproteins; cholesterol; cardiovascular disease; autophagy

Introduction

HDL serves a prominent anti-atherogenic function by mediating RCT. RCT is initiated by the association of apoA-I in lipid-poor HDL particles with the ATP-binding cassette transporter A1 (ABCA1) on macrophages and other target cells (1). This interaction allows HDL to act as an acceptor for cholesterol. Lipid-poor HDL can subsequently be converted to a “mature” HDL particle *via* the action of the HDL-associated enzyme lecithin-cholesterol acyltransferase (LCAT). LCAT activation converts HDL from a nascent discoidal to a mature spherical form and thus increases the cholesterol carrying capacity of the particle. Mature HDL is thought to mediate cholesterol efflux *via* an interaction with the ABCG1 transporter

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(1). The subsequent binding of apoA-I containing HDL particles to the scavenger receptor B1 (SRB1) on hepatocytes permits the unloading of cholesterol which is ultimately secreted as bile (2, 3). By this mechanism, HDL is thought to attenuate inflammatory injury and reduce atheroma formation (4).

In addition to apoA-I, HDL also serves as a carrier for other exchangeable apolipoproteins, regulatory proteins and anti-oxidant enzymes. Recent proteomic analyses have revealed that more than 85 proteins may associate with HDL particles (5). This observation suggests that HDL subspecies exist that subserve a variety of cellular functions (5). Indeed, it is now appreciated that HDL possesses prominent anti-inflammatory and anti-oxidant properties that are independent of its ability to efflux cholesterol (6-8). Paraoxonase 1 (PON1) and platelet-activating factor acetylhydrolase (PAF-AH) are esterases that bind to helical regions of apoA-I (9). These enzymes are important anti-oxidant enzymes that catalyze the hydrolysis of oxidized phospholipids (10). Data also suggest that the HDL-associated lysosphingolipid sphingosine 1-phosphate exerts anti-inflammatory effects. Thus, both protein and lipid components of HDL may help to maintain cellular homeostasis. The observation that circulating levels of HDL inversely correlate with mitochondrial DNA damage in humans suggest a specific role for HDL in maintaining mitochondrial integrity (11).

Hypercholesterolemia is a major, cardiovascular risk factor which contributes to the pathogenesis of atherosclerosis, metabolic syndrome and diabetes. Chylomicrons, VLDL and LDL are apoB-containing lipoproteins that serve an important function by delivering cholesterol and triglycerides to peripheral cells. These particles, however, are susceptible to oxidative modification and may adopt pro-atherogenic properties. The uptake of oxidized LDL (oxLDL) by intimal macrophages is a well-characterized component of atherosclerotic plaque formation (12, 13). Mitochondria are principal sites of ROS formation in the cell and are also targets for redox injury (11, 14-18). An increase in plasma cholesterol and triglycerides has been implicated in the development of mitochondrial dysfunction (19). Lysophosphatidylcholine (lysoPC), a pro-inflammatory lipid associated with oxLDL, induces mitochondrial ROS formation and increases permeability in intact cells and isolated mitochondria (20-22). These responses are also induced by I-R injury. An increase in oxidant formation thus damages mitochondrial structural elements and impairs respiration by reducing oxidative phosphorylation and ATP formation (23). Irreversible damage occurs upon dissipation of mitochondrial membrane potential ($\Delta\Psi m$) and opening of the mitochondrial permeability transition pore (mPTP). HDL possesses anti-inflammatory and anti-oxidant properties that protect mitochondria from injury. The goal of this chapter will be to discuss mechanisms by which HDL-associated proteins and lipids modulate mitochondrial function and improve cell survival.

Mitochondrial Structure and Function

The mitochondrion is an energy producing organelle that generates ROS and heat as byproducts of oxidative phosphorylation (24). Mitochondria are found in all tissues but are most abundant in those with high metabolic requirements, such as cardiac and skeletal muscle (25). The mitochondrion is a double membraned organelle that contains its own

maternally-inherited DNA (26, 27). The oxidative phosphorylation complexes; Complex I *(NADH: ubiquinone oxidoreductase)*, Complex II *(succinate dehydrogenase)*, Complex III *(CoQH2-cytochrome c reductase)*, Complex IV *(cytochrome c oxidase)*, and Complex V *(ATP synthase)*, are encoded by both the nuclear and mitochondrial genomes. Mitochondria utilize both electron and proton gradients in order to produce energy, in the form of ATP, while consuming oxygen. Electrons enter the electron transport chain at Complexes I and II and are then passed to Complex III *via* the Q cycle on coenzyme Q (28). Electrons are shuttled to Complex IV where cytochrome c is reduced. As oxygen is consumed at Complex IV, cytochrome c is reoxidized, and water is formed. As the electrons are shuttled through the complexes, hydrogen ions are pumped from the mitochondrial matrix by Complexes I, III, and IV into the intramembrane space, thus establishing a protomotive force. As the protons flow down the gradient from the intermembrane space back into the mitochondrial matrix, ATP is produced at Complex V (27, 29).

The measurement of mitochondrial respiration can be performed using an oxygen electrode in isolated organelles. Chance and Williams defined the different states of mitochondrial respiration by measuring oxygen consumption in the presence of various mitochondrial substrates (30). Under control conditions, mitochondria remain in state 3.5 respiration, where there is a generous supply of substrates for the electron transport chain and ADP for ATP production. Using the oxygen electrode, State 3 respiration was defined as the amount of oxygen consumed in the presence of pyruvate, succinate and ADP. State 4 respiration represents oxygen consumption after ADP has been fully converted to ATP. Currently, extracellular flux analysis represents state-of-the-art technology for the measurement of mitochondrial function in whole cells rather than isolated mitochondria. Endogenous substrates required for respiration are found within the cell. Under these conditions, inhibitors of the mitochondrial complexes can be administered to cells in order to determine different indices of mitochondrial function including: basal and maximal mitochondrial respiration; oxygen consumption required for ATP production; proton leak; and non-mitochondrial oxygen consumption (31). Development of this technology has revolutionized the field of mitochondrial biology (31, 32).

Under normal physiological conditions, some electrons may spill off of the electron transport chain and react with oxygen to form superoxide anion. Complexes I and III are the principal sources of ROS during oxidative phosphorylation (33). At low levels of production, ROS can act as signaling molecules. When produced in excess, however, ROS induce peroxidation of cellular lipids and proteins, damage mitochondrial and nuclear DNA and impair cell division. It follows that mitochondrial oxidative phosphorylation is significantly impaired. Bioenergetic dysfunction ensues and is associated with dissipation of $\Delta\Psi m$ and opening of the mPTP (34). mPTP induction subsequently leads to mitochondrial swelling and cell death (24, 33). The antioxidant enzyme manganese superoxide dismutase is present in mitochondria and reduces superoxide to hydrogen peroxide, thus minimizing injury. The ability of the mitochondria to clear ROS thus increases cell survival. Schriner and colleagues reported that overexpression of mitochondrially targeted catalase in cardiac and skeletal muscle resulted in an increase in murine longevity (35). Mitochondrial DNA damage in myocytes, as assessed by 8-hydroxyguanosine (8-OhdG) formation, increased with age but was attenuated by catalase overexpression in these mice (35). Atherosclerosis and I-R injury

are common cardiovascular disorders that are associated with the development of mitochondrial dysfunction. Defects in electron transport and oxidative phosphorylation enhance ROS formation resulting in mitochondrial injury and the induction of apoptosis *via* the cleavage of caspase 9. In a mouse model of myocardial infarction, ROS production damages both mitochondrial DNA and proteins, resulting in decreased enzymatic activities of mitochondrial Complexes I, III and IV (36). Further, coronary I-R injury is associated with opening of the mPTP leading to cell death (37). Ongoing studies are assessing the effects of mitochondrially-targeted antioxidant therapies on the development and progression of cardiovascular disease (38).

Mitochondrial Clearance

Cells utilize a mitochondrial clearance mechanism termed autophagy in order to avoid cell death secondary to injurious stimuli. The term autophagy was coined by Christian De Duve in the 1960s and is derived from the Greek words auto (self) and phagy (eating) (24, 39, 40). Today, we know that there are three main types of autophagy: 1) macroautophagy (usually termed autophagy); 2) chaperone mediated autophagy; and 3) microautophagy (41). Autophagy was first characterized as a response to nutrient starvation and was found to be associated with inactivation of the mammalian target of rapamycin (mTOR) (24, 39, 40). Autophagy breaks down macromolecules and recycles their components not only to preserve cellular energy but also to clear damaged proteins and mitochondria (24, 39, 40). More than 30 AuTophagy-related Genes (ATG) are conserved from yeast to mammals and participate in autophagy at different steps throughout the process (42, 43).

Mitochondria can be cleared through macroautophagy, but have also been shown to utilize different ATG proteins to selectively remove damaged mitochondria *via* mitophagy (44). As noted above, mitochondria contain their own genome which lacks compact chromatin structure and, compared to nuclear DNA, have a less effective replication and repair system (45). Further, since mitochondria are the primary cellular producer of ROS, and the mitochondria contains highly reactive iron sulfur clusters, mitochondria are 10-20 times more likely to accumulate DNA damage compared to nuclear DNA. Mitophagy is controlled either in conjunction with general macroautophagy or selectively through specific mitophagy genes. AMPK is activated in response to decreased intracellular ATP, and then phosphorylates the Atg1 homologs ULK1 and ULK2 to activate both general macroautophagy and mitophagy (46). AMPK or ULK1 deficient hepatocytes exhibit accumulation of p62, ubiquitin aggregates and abnormal mitochondria (46). In the context of atherosclerosis and I-R injury, mitochondria are damaged and are more likely to produce ROS and less ATP. Mitophagy plays an important role in attenuating apoptosis or necrosis by clearing damaged mitochondria. This prevents the release of cytochrome c, apoptosis-inducing factor (AIF) and other apoptotic factors that can cause the cell to swell and burst. Mitochondrial turnover is thus essential for cell survival.

Mitochondria isolated from rodent hearts have an average half-life of 16-18 days (47). In rodents exposed to hypoxic conditions, it was shown that mitochondrial half-life is reduced and is associated with a decrease in cardiac cytochrome c content. Further, there was an increase in mitochondrial biogenesis suggesting that formation of new mitochondria is an

important response to I-R injury (48). It is well known that starvation can induce both macroautophagy and mitophagy, but more recent data suggest that autophagy and mitophagy can be initiated by ischemia (44, 49, 50). The induction of autophagy is essential for the protective effects of ischemic pre- and post- conditioning in the heart (51-53). Parkin, pink1 and related proteins play an important role in mitophagy and mitochondrial turnover (54). In parkin- and pink1-deficient mice, there is an exacerbation of I-R injury, suggesting that the clearance of damaged mitochondria is an essential component of ischemic pre-conditioning (55, 56). Since mitochondrial biogenesis and turnover are tightly regulated and have major effects on outcomes, further treatments for heart disease should utilize these pathways in drug discovery.

Mitochondria and Cell Survival Mechanisms

Cardiac ischemia arises in response to unstable angina and acute myocardial infarction (57). Upon reperfusion, significant injury occurs at the level of the mitochondrion (57-59). Due to the high energy demands of the heart, I-R injury significantly impairs mitochondrial respiration. This is associated with increased ROS formation, uncoupling of oxidative phosphorylation and opening of the mPTP (60). mPTP opening is associated with dissipation of the $\Delta\Psi m$, calcium influx and the release of pro-apoptotic factors (59, 61). Ischemic pre-conditioning and post-conditioning have been shown to preserve mitochondrial function thus reducing myocardial reperfusion injury (62-64). These conditioning protocols are characterized by brief disruption of blood flow prior to sustained ischemia and reperfusion and result in the activation of two major cell survival pathways (62-64). The Reperfusion Injury Salvage Kinase (RISK) pathway is comprised of the pro-survival kinases phosphatidylinositol 3-kinase (PI3K), protein kinase B (*Akt*) and extracellular regulated kinase 1/2 (ERK1/2) (58, 65-68). These enzymes phosphorylate multiple substrates in the cell that converge to inhibit opening of mPTP (65, 69-72). Glycogen synthase kinase 3 beta (GSK3β) appears to be an important target for RISK-dependent cardiomyocyte survival (65, 73). Phosphorylation of GSK3β reduces its enzymatic activity. Inactive GSK3β attenuates mitochondrial injury by increasing Bcl-2 anti-apoptotic activity, inhibiting the translocation of pro-apoptotic Bax to the outer mitochondrial membrane and preventing mPTP induction *via* stabilization of the mPTP regulatory protein cyclophilin D (69, 74). The Survivor Activating Factor Enhancement (SAFE) cascade is an alternate pathway for mitochondrial preservation (58, 75). TNFα activates the SAFE pathway by binding to TNF receptor type 2 (TNFR2) (58, 76). TNFR2 engagement results in the activation of Janus kinase (JAK) which phosphorylates the signal transducer and activator of transcription 3 (STAT3) (58). The SAFE pathway has been shown to reduce infarct size in animals undergoing I-R injury by a mechanism involving STAT3 phosphorylation and inhibition of mPTP opening (77). While the RISK and SAFE pathways preserve mitochondrial function by increasing the activity of specific signaling intermediates, data suggest that crosstalk between these pathways occurs, with stabilization of the mPTP as a final common outcome (62, 75).

HDL And ApoA-I Preserve Mitochondrial Function

Lipid peroxides present in oxLDL have been shown to stimulate ROS formation and impair oxygen consumption at Complexes I, II/III, and IV of the respiratory chain, resulting in

mitochondrial dysfunction (78, 79). The HDL-associated protein PON1 performs an important antioxidant function by hydrolyzing cholesteryl esters and phospholipids in oxidized lipoproteins (79). PON1 may thus preserve mitochondrial function due to its ability to degrade oxidized lipid species. In contrast to this indirect effect of HDL-associated PON1, a direct role for apoA-I and the lysosphingolipid sphingosine 1-phosphate (S1P) in mediating cardiomyocyte survival has been reported (78-81). Infarct size in apoA-I$^{-/-}$ mice undergoing coronary artery ligation/reperfusion is significantly increased compared to lesions in wildtype mice (82). This correlated with a reduction in Coenzyme Q (CoQ) in mitochondria isolated from apoA-I$^{-/-}$ mice. CoQ deficiency was associated with a significant reduction in electron transfer from Complex II to Complex III (82). In related studies, it was shown that exogenous administration of CoQ restored mitochondrial CoQ levels and attenuated infarct size in apoA-I$^{-/-}$ mice (82). These results suggested that apoA-I plays a key role in maintaining the coupling of electron transport proteins.

Data suggest that HDL, similar to ischemic pre-conditioning and post-conditioning, prevents mitochondrial injury *via* activation of RISK and SAFE survival cascades (83). The SAFE pathway influences mitochondrial function in several ways. First, STAT3-mediated nuclear transcription results in up-regulation of anti-apoptotic Bcl-2 and the antioxidant genes manganese superoxide dismutase and metallothionein while inhibiting pro-apoptotic Bax/Bad expression (62, 84). STAT3 has also been shown to regulate the electron transport chain and mitochondrial respiration (84, 85). STAT3 gains access to the mitochondrion with the assistance of the chaperone protein GRIM-19 (86). At this locus, STAT3 inhibits Complex I and II respiration and the release of cytochrome c (84). It is proposed that STAT3 ultimately protects mitochondria by reversibly uncoupling electron flow between respiratory complexes, reducing ROS formation and preventing mPTP induction (84, 87-89). Administration of apoA-I to rodents prior to coronary artery occlusion attenuates morphologic changes associated with ischemic injury and reduces infarct size (83). Consistent with known targets of the RISK and SAFE signaling cascades, apoA-I treatment increased the phosphorylation of *Akt* and GSK3β. The infarct-sparing response to apoA-I was significantly reduced in animals treated with inhibitors of *Akt*, ERK1/2 and JAK/STAT (83). These data suggested that the inhibitory effect of apoA-I on myocardial infarct size was due to activation of both RISK and SAFE survival pathways, resulting in attenuation of mitochondrial injury.

HDL-Associated Sphingosine 1-Phosphate Influences Mitochondrial Function

The lipid composition of HDL plays an important role in determining the function of the lipoprotein particle (90, 91). Lipid species maintain the structural integrity of HDL and regulate the activities of HDL-associated proteins (92). Data suggest that the lysosphingolipid S1P of HDL plays an important role in cardioprotection. While S1P is synthesized in hematopoietic and endothelial cells, HDL serves as its principal carrier in plasma (93-95). S1P has been shown to act as an inducer of both the RISK and SAFE pathways (80, 96, 97). Cardiomyocyte responses to S1P actions are mediated by multiple receptor isoforms (S1P1, S1P2 and S1P3) (80, 98-100). Addition of HDL or purified S1P to

neonatal rat cardiac cardiomyocytes activates S1P2 receptors resulting in STAT3 phosphorylation. In contrast, HDL that is depleted of S1P fails to support STAT3 phosphorylation (96). HDL treatment was shown to activate *Akt* and ERK1/2 pathways *via* distinct S1P receptors in mouse cardiomyoctyes exposed to hypoxia-reoxygenation (98). S1P1 binding resulted in activation of ERK1/2, while S1P3 induced *Akt* activation. Under these conditions, levels of phosphorylated GSK3β, a known inhibitor of mPTP opening, were increased (98). This response was inhibited by S1P receptor blockers and the PI3K inhibitor wortmannin, suggesting that S1P reduces cardiomyocyte injury by activating the RISK pathway (98). Numerous *in vivo* studies support a role for S1P in the activation of RISK and SAFE signaling cascades in the context of I-R injury and heart failure (80, 98, 101-103).

Cardioprotective responses to HDL and S1P are ultimately mediated at the level of the mitochondrion. Administration of HDL to mice undergoing I-R injury reduces infarct size in a concentration-dependent manner (104). This response was associated with STAT3 phosphorylation and inhibition of mPTP opening in isolated cardiomyocytes. Protective effects at the level of the mitochondrion were abolished in TNFα$^{-/-}$ and cardiomyocyte-specific STAT3$^{-/-}$ mice, suggesting that STAT3 mediates the activation of the SAFE pathway (105). Forkhead box O-1 (FOXO-1) is a transcription factor that is known to increase ROS formation and apoptosis in the non-phosphorylated state (106). While the RISK pathway and PI3K/*Akt* activation are associated with the inactivation of FOXO-1, data suggest that the SAFE survival pathway also modulates FOXO-1 activity (100, 106). S1P stimulated the nuclear phosphorylation/inactivation of FOXO-1 in a manner that was blocked by both a JAK/STAT3 and PI3K inhibitor (100). These observations suggest that the S1P-dependent phosphorylation of FOXO-1 may represent a point of convergence for the RISK and SAFE survival cascades.

Finally, data show that S1P regulates Complex IV assembly and cellular respiration in mitochondria through an interaction with mitochondrial prohibitin-2 (PHB2) (107, 108). PHB2 is a scaffold protein which functions to stabilize the structure of the inner mitochondrial membrane (109). Disruption of S1P-PHB2 binding abolishes the cardioprotective response of cardiomyocytes to ischemic pre-conditioning. Under this condition, a reduction in oxidative phosphorylation was associated with opening of mPTP and mitochondrial injury (59, 72). These data, therefore, suggest that S1P and PHB2 stabilize Complex IV and reduce ROS formation while also supporting oxidative phosphorylation (107).

HDL and Autophagy Induction

Mitochondrial damage induced by I-R injury releases apoptotic factors that damage neighboring mitochondria. It has been proposed that autophagy serves a cytoprotective role by clearing damaged mitochondria and limiting potentially deleterious effects on neighboring organelles (110, 111). Ischemia initiates autophagy by inducing the de-phosphorylation and inactivation of mTOR which normally acts as a suppressor of autophagy (112, 113). An increase in the ratio of AMP/ATP concurrently induces AMP-activated protein kinase (AMPK) and stimulates autophagy *via* multiple mechanisms. The

vacuolar protein sorting-34 (Vps34) is a class III PI-3 kinase that initiates phagophore formation through its association with beclin1 (113). This pre-autophagosomal structure engulfs cytoplasmic components, including damaged mitochondria. Phosphatidylethanolamine (PE) and microtubule-associated protein light chain-3 (LC3 I) interact to form the conjugated product LC3 II. LC3 II and the adaptor protein p62 are recruited to yield the mature autophagosome (112). The autophagosome then fuses with lysosomes where ingested products are digested. Inhibitors of autophagy promote ROS formation and aggravate mitochondrial injury in response to I-R (114). They have also been shown to negate cell survival mechanisms associated with ischemic pre-conditioning. It follows that autophagy contributes to the cytoprotection associated with pre-conditioning (52, 115). A role for S1P in the inhibition of mTOR and activation of autophagy has been reviewed (116, 117). It follows that inhibitors of S1P formation also prevent the induction of autophagy (118). As the principal carrier of S1P, HDL may induce autophagy as a cell survival mechanism. In support of this, it was shown that HDL inhibits mTOR activity, stimulates the expression of LC3 II and stimulates the formation of autophagosomes (119).

Alternate Apolipoproteins and Mitochondrial Function

In addition to apoA-I and apoB, other apolipoproteins (i.e., apoJ, apoM, apoC and apoO) serve as regulatory molecules for cholesterol homeostasis (120). Recent data also suggest a role for these apolipoproteins in the regulation of mitochondrial function. ApoJ, also known as clusterin, is a glycoprotein expressed ubiquitously during development and in adults and is associated with small, dense HDL3 particles (121-123). Due to the presence of disulfide bonds, apoJ possesses antioxidant properties that inhibit ROS-dependent injury and preserve mitochondrial function (24). In the H9c2 cardiomyocyte cell line, it was shown that apoJ protects against ROS-induced apoptosis by activating *Akt* and GSK-3β, thus suggesting a role in the activation of the RISK survival cascade (124).

ApoM is apolipoprotein that accounts for approximately 5% of the protein content of HDL. A major function of apoM is to attenuate atherosclerosis by stimulating the formation of small, dense preβ-HDL particles that play an important role in RCT (125-128). ApoM protects mitochondrial function by virtue of its ability to bind to S1P and facilitate its incorporation into HDL (101, 127, 129, 130). The relationship between apoM and S1P-mediated cardioprotection has been evaluated in a murine model of I-R injury (131). Over-expression of apoM in mice was accompanied by a significant reduction in myocardial infarct size and leukocyte accumulation (131). The underlying mechanism of apoM-S1P-induced cardioprotection was due to inhibition of cardiomyocyte cell-cell coupling (131). The passage of death signals through gap junctions was reduced, resulting in attenuation of I-R-induced cardiomyocyte injury (131).

ApoC is an exchangeable apolipoprotein associated with HDL as well as apoB-containing lipoproteins. Three structurally distinct isoforms (apoC-I, apoC-II and apoC-III) have been identified that exert differential effects on lipid metabolism, ROS formation, mitochondrial function and cell death. (132). Panin and colleagues have tested effects of these apoC isoforms on oxidative phosphorylation in rat liver mitochondria (133). Using palmitoyl carnitine as a substrate for oxidative phosphorylation, it was shown that apoC-III, but neither

apoC-I nor apoC-II, inhibited State 3 respiration (133). At higher concentrations of apoC-III, the rate of oxygen consumption was reduced ~70%, and oxidative phosphorylation was completely blocked (133). These data were the first to show an inhibitory effect of ApoC-III on mitochondrial function. Other data support a role for apoC-I in the development of mitochondrial injury in human aortic smooth muscle cells (134). Enrichment of HDL with apoC-I was shown to induce cell death in a neutral sphingomyelinase (N-SMAS) dependent manner, with the production of ceramide from N-SMAS stimulating the release of cytochrome c from the mitochondria, the cleavage of caspase 3 and apoptosis. The increased cell death of the aortic smooth muscle cells incubated with ApoC-I may account for the unstable plaque formation seen in patients with hypercholesterolemia (134). Interestingly, apoC-I enrichment of HDL was associated with a reduction in HDL-associated apoA-I, suggesting that loss of apoA-I and its cytoprotective effects is a component of apoC-I mediated apoptosis (134).

Apoliprotein O is a 198 amino acid protein which is found in association with HDL, LDL and VLDL particles (135). ApoO is up-regulated by metabolic stress in the diabetic heart where it is thought to play a role in reducing myocardial injury by preventing macrophage lipid accumulation (135). ApoO and the related apoO-like protein have also been shown to stabilize the inner mitochondrial membrane and the cristea (136-138). In contrast to this report, over-expression of apoO was shown to impair cardiac function and degrade mitochondrial structure in cardiomyocytes of hypercholesteroleic mice (139). This observation suggested a pathogenic role for apoO in obesity. To further understand the pathogenic mechanism of apoO, Turkeih and colleagues developed a stable cardiac myoblast cell line that overexpressed apoO. These cells were characterized by an increase in mitochondrial respiration, fatty acid uptake and metabolism, ROS formation and apopotosis compared to control cells (139). It was suggested that an increase in apoO expression promotes the transition from mitochondrial dysfunction to the development of overt cardiomyopathy (139). Further research is required to delineate the role of apoO in diverse cardiovascular pathologies.

Conclusion

While HDL plays an important anti-atherogenic role by mediating RCT, it is also an active signaling particle that possesses anti-inflammatory, anti-oxidant and anti-apoptotic properties. HDL-associated proteins and lipids play an important role in the preservation of mitochondrial function. The anti-oxidant enzyme PON1 prevents damage to respiratory complexes by degrading oxidized lipids such as lysoPC (140). ApoA-I also protects mitochondria by multiple mechanisms. Through an interaction with CoQ, apoA-I stabilizes complex II and inhibits ROS-mediated damage to respiratory complexes (82). ApoA-I and the HDL- associated lipid S1P also protect mitochondria via the activation of RISK and SAFE survival pathways (83). *Akt*, ERK1/2 and JAK/STAT3 are critical mediators of these cell survival cascades. The cytoprotective response to S1P is due to an interaction with cellular S1P receptors, resulting in activation of JAK/STAT3 signaling. Binding of apoA-I to ABCA1 is also reported to activate STAT3 signaling and attenuate inflammatory injury (141). It has been proposed that phosphorylated FOXO-1 and GSK3β are final, common effectors of these pathways and improve cell survival by attenuating mitochondrial ROS

formation, mPTP induction and apoptosis (100, 142). Autophagy represents an additional survival mechanism activated by apoA-I. Under these conditions, ROS-dependent injury may be reduced *via* the effective clearance of damaged mitochondria.

The ability of HDL to preserve mitochondrial function may be attenuated under pathological conditions. A reduction in circulating HDL concentration is associated with a number of inflammatory disorders (143, 144). Under these conditions, depletion of apoA-I, PON1, apoM and apoJ from HDL particles may result in a loss of function (143, 145-148). A decrease in apoM may ablate the protective effects of S1P on mitochondrial function. This response may augment the vascular leakage observed in patients with sepsis (149). Lipoprotein oxidation is also associated with a reduction in S1P levøs and accumulation of pro-inflammatory lysoPC in HDL particles (150). With respect to apoJ, a decrease in its association with HDL has been implicated in the development of insulin resistance and an increase in apoptosis (151). Finally, an increase in the incorporation of apoC in the HDL particle may increase mitochondrial injury and apoptosis. Under these conditions, HDL function may be further degraded by the displacement of apoA-I by apoC. These observations suggest that raising circulating HDL concentration as well as its functional properties represents an important therapeutic strategy to minimize mitochondrial injury.

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