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High-density lipoprotein, mitochondrial dysfunction and cell survival mechanisms

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ABSTRACT

Ischemic injury is associated with acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting and open heart surgery. The timely re-establishment of blood flow is critical in order to minimize cardiac complications. Reperfusion after a prolonged ischemic period, however, can induce severe cardiomyocyte dysfunction with mitochondria serving as a major target of ischemia/reperfusion (I/R) injury. An increase in the formation of reactive oxygen species (ROS) induces damage to mitochondrial respiratory complexes leading to uncoupling of oxidative phosphorylation. Mitochondrial membrane perturbations also contribute to calcium overload, opening of the mitochondrial permeability transition pore (mPTP) and the release of apoptotic mediators into the cytoplasm. Clinical and experimental studies show that ischemic preconditioning (IC_{PRE}) and postconditioning (IC_{POST}) attenuate mitochondrial injury and improve cardiac function in the context of I/R injury. This is achieved by the activation of two principal cell survival cascades: 1) the Reperfusion Injury Salvage Kinase (RISK) pathway; and 2) the Survivor Activating Factor Enhancement (SAFE) pathway. Recent data suggest that high density lipoprotein (HDL) mimics the effects of conditioning protocols and attenuates myocardial I/R injury *via* activation of the RISK and SAFE signaling cascades. In this review, we discuss the roles of apolipoproteinA-I (apoA-I), the major protein constituent of HDL, and sphingosine 1-phosphate (S1P), a lysosphingolipid associated with small, dense HDL particles as mediators of cardiomyocyte survival. Both apoA-I and S1P exert an infarct-sparing effect by preventing ROS-dependent injury and inhibiting the opening of the mPTP.

1. Introduction

A principal function of HDL is to mediate reverse cholesterol transport, a process by which excess cholesterol is removed from non-hepatic tissues and transferred to the liver for metabolism and excretion into the bile (Lewis and Rader, 2005; Fazio and Linton, 2006). HDL also possesses anti-inflammatory and antioxidant properties that are attributed, in large part, to its major protein constituent apoA-I (Ansell et al., 2005; Assmann and Nofer, 2003; Dunbar and Rader, 2005; Navab et al., 2003a). Helical regions of apoA-I serve as a platform for the binding of antioxidant proteins, including paraoxonase 1 (PON1) and platelet-activating factor acetylhydrolase (PAF-AH) (Gu et al., 2016; Bashtovyy et al., 2011). These enzymes play an important role by degrading cholesteryl esters and phospholipids in oxidized lipoproteins. A recent study shows that the HDL proteome consists of more than 85 proteins (Shah et al., 2013). It follows that HDL is a heterogenous particle and that HDL subspecies may display discreet functional properties.

The lipid composition of HDL is also an important determinant of its function (Ashby et al., 2001; Baker et al., 1999). Lipid species maintain the structural integrity of HDL and regulate the activities of HDL-associated proteins (Weisner et al., 2009). Among the phospholipids, phosphatidylcholine, sphingomyelin (SM) and sphingosine 1-phosphate (S1P) are well represented. S1P is synthesized in hematopoietic and endothelial cells through the action of sphingosine kinase 1 (SphK1) (Yatomia et al., 2001; Venkataraman et al., 2008). HDL takes up S1P and serves as its principal carrier in plasma (Kontush et al., 2007; Yatomi et al., 2001). Anti-inflammatory and antioxidant properties are prominently exhibited by small, dense HDL particles including preβ-HDL and HDL3 (Kontush et al., 2007). This is due, in part, to the

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increased ratio of S1P to SM in HDL3 particles compared to more buoyant HDL1 and HDL2 particles.

Many of the salutary effects of HDL on cardiac and vascular function have been ascribed to the presence of S1P in the lipoprotein particle while other responses to HDL are S1P-independent (Sattler and Levkau, 2009; Tao et al., 2010). HDL-bound S1P is significantly reduced in patients with coronary artery disease (CAD) compared to healthy controls (Sattler et al., 2010, 2015). A corresponding increase in non-HDL-bound S1P is associated with an increase in the severity of CAD symptoms (Sattler et al., 2010). In light of these findings, HDL isolated from CAD patients displays impaired S1P-dependent signaling responses under in vitro conditions (Sattler et al., 2015). Supplementation of HDL from CAD patients with S1P, however, effectively restores the functional properties of HDL-bound S1P (Sattler et al., 2015).

Cardiac ischemia arises in response to pathological events including acute myocardial infarction (AMI), unstable angina and thrombolysis as well as surgical procedures (Verma et al., 2002). Reperfusion results in the activation of deleterious signaling pathways, with the mitochondrion serving as a critical site of injury (Verma et al., 2002; Lecour, 2009; Perrelli et al., 2011). The prompt re-establishment of coronary blood flow is thus critically required to minimize myocardial infarct size (Verma et al., 2002; Perrelli et al., 2011; Hausenloy and Yellon, 2004). In light of the high energy demands of the heart, ischemia/reperfusion (I/R) is associated with degradation of mitochondrial bioenergetics. An increase in reactive oxygen species (ROS) formation and uncoupling of oxidative phosphorylation are early events followed by opening of the mitochondrial permeability transition pore (mPTP) (Hill et al., 2012). The mPTP is a high conductance channel spanning the inner and outer mitochondrial membranes that remains in a closed state under normal conditions (Perrelli et al., 2011; Heusch et al., 2010). mPTP opening occurs in response to I/R injury and is associated with dissipation of the mitochondrial membrane potential (ΔYm), calcium influx and the release of pro-apoptotic factors (Perrelli et al., 2011; Heusch et al., 2010). Minimizing mitochondrial damage is clearly an important strategy for maintaining normal cardiac function. Ischemic pre-conditioning (IC_{PRE}) and post-conditioning (IC_{POST}) have been shown to reduce myocardial injury upon sustained reperfusion (Lecour, 2009; Vinten-Johansen et al., 2005,2007). IC_{PRE} and IC_{POST} are characterized by repetitive, brief episodes of ischemia and reperfusion performed either prior to or after a prolonged period of ischemia (Vinten-Johansen et al., 2005, 2007). Both conditioning procedures protect the heart by activating cell survival pathways that converge at the level of the mitochondrion. HDL has also been shown to improve cardiac function in the context of I/R injury by preventing defects in mitochondrial function. The goal of this review is to discuss survival pathways activated by HDL that preserve myocardial function in the context of I/R injury.

2. Mitochondria and cellular bioenergetics

Mitochondria are abundant in tissues with a high metabolic demand including cardiac and skeletal muscle (Forner et al., 2006). These organelles are characterized by a double-membrane structure separated by an intermembrane space. Respiratory complexes located in the inner mitochondrial membrane utilize oxidative phosphorylation to generate energy in the form of ATP. Nicotinamide adenine dinucleotide (NADH) initially serves as an electron donor for complex I (NADH:ubiquinone oxidoreductase) which transfers electrons to ubiquinone (Sazanov, 2015). Complex II (succinate dehydrogenase) functions in parallel with complex I and transfers electrons from succinate to ubiquinone. Electrons are subsequently shuttled from complexes I and II to complex III (CoQH2-cytochrome c reductase) via coenzyme Q and the Q cycle (30). Cytochrome c (cyt c) is a protein located in the intermembrane space that supports mitochondrial respiration by shuttling electrons from complex III to complex IV (cytochrome c oxidase) coincident with cyt c reduction (Chen et al., 2010). As oxygen is consumed at complex IV, cyt c is re-oxidized and water is formed. Throughout this process, hydrogen ions derived from complexes I, III, and IV are pumped from the matrix into the intermembrane space. As hydrogen ions accumulate at this site, a proton gradient is established which gives rise to $\Delta\Psi$m (Amo et al., 2011). Finally, complex V (ATP synthase) utilizes the energy stored in the proton gradient to generate ATP. While electron transfer is tightly regulated, some electrons may react with oxygen to form superoxide anion. Deleterious effects of superoxide, however, are minimized by the presence of manganese superoxide dismutase which reduces superoxide to hydrogen peroxide. Under conditions where reactive oxygen species (ROS) are formed in excess, damage to mitochondrial structural components and DNA occurs.

3. Mitochondrial responses to ischemia/reperfusion injury

Mitochondrial dysfunction is a hallmark of I/R injury. Damage to mitochondria is initiated during the ischemic period and becomes amplified during reperfusion (Kalogeris et al., 2012; Chen et al., 2007; Becker, 2004; Pell et al., 2016). Recent data suggest that the complex II substrate succinate accumulates during ischemia, and, upon reperfusion, electron transport operates in the reverse mode with significant quantities of superoxide being generated at complex I (Pell et al., 2016). Ischemic injury at the level of complex III also plays an important role in stimulating ROS formation at sites upstream in the electron transport chain (Chen et al., 2010; Chen et al., 2006; Lesnefsky et al., 2004). ROS, generated in this manner, induce damage to mitochondrial respiratory complexes, structural components and DNA (Becker, 2004; Casillas-Ramirez et al., 2006; Jaeschke and Mitchell, 1989; Singer and Brealey, 1999). Cardiolipin and cyt c are critical sites of ROS-dependent injury. Cardiolipin is a phospholipid in the inner mitochondrial membrane that stabilizes respiratory proteins, in part, by forming a complex with cyt c (Chen et al., 2010). An increase in ROS formation induces the peroxidation of the cardiolipin-cyt c complex resulting in the release of cyt c into the cytosol (Chen et al., 2010). The loss of cyt c facilitates apoptosis, inhibits respiration at complex IV and stimulates further generation of ROS (Chen et al., 2006; Lesnefsky et al., 2004; Lemasters and Holmuhamedov, 2006). It follows that tissue oxygen utilization and ATP formation are severely impaired, and apoptotic/necrotic mechanisms are activated (Fink, 2001).

The ability of mitochondria to respond to fluctuations in cytosolic calcium ($Ca2^+$) concentration is an important indicator of mitochondrial quality (Lemasters et al., 2009; Rodriguez-Enriquez et al., 2004). Healthy mitochondria take up calcium via the uniporter located on the inner membrane and release calcium under normal conditions via the $Na^+/Ca2^+$ antiporter. However, this pathway is vulnerable to bioenergetic dysfunction and can result in accumulation of mitochondrial calcium. During reperfusion, mPTP opening is stimulated by numerous factors including ROS, calcium overload and dissipation of $\Delta\Psi$m (Wong et al., 2012). Induction of mPTP results in calcium release, mitochondrial swelling and apoptotic cell death (Lemasters et al., 2009; Wong et al., 2012; Bopassa et al., 2005; Kim et al., 2008; Juhaszova et al., 2009; Chopra et al., 2011; Tammineni et al., 2013). These responses are negatively correlated with cardiomyocyte survival (Juhaszova et al., 2009).

4. Pre- and post-conditioning attenuate ischemia-reperfusion injury

IC_{PRE} and IC_{POST} describe intermittent episodes of I/R prior to sustained ischemia and reperfusion, respectively (Vinten-Johansen