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Cardioprotective Role of Caveolae in Ischemia-Reperfusion Injury

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Abstract

Caveolae are flask-like invaginations of the plasma membrane enriched in cholesterol, sphingolipids, the marker protein caveolin and the coat protein cavin. In cardiomyocytes, multiple signaling molecules are concentrated and organized within the caveolae to mediate signaling transduction. Recent studies suggest that caveolae and caveolae-associated signaling molecules play an important role in protecting the myocardium against ischemia-reperfusion injury. For example, cardiac-specific overexpression of caveolin-3 has been shown to lead to protection that mimics ischemic preconditioning, while the knockout of caveolin-3 abolished ischemic preconditioning. In this review, we discuss the molecular mechanisms and signaling pathways that are involved in caveolae-mediated cardioprotection, and examine the potential for caveolae as a therapeutic target for pharmaceutical intervention to treat cardiovascular disease.

Keywords: Caveolae; Cardioprotection; Ischemia-reperfusion

Introduction

Ischemia-reperfusion (I/R)-induced myocardial cell death is a major cause of morbidity and mortality in heart disease. Ischemia leads to ATP depletion and a rise in intracellular calcium (Ca^{2+}), which induces mitochondrial Ca^{2+} accumulation. The duration of ischemia is a critical factor in determining ischemic injury and cell fate. Although the reintroduction of oxygen upon reperfusion allows for ATP production to resume, there is a burst of reactive oxygen species (ROS) that occurs because of damage to electron transport chain components and mitochondrial Ca^{2+} overload. This triggers the opening of the mitochondrial permeability transition pore and further compromises myocardial energetics. Therefore, mitochondria are thought to be a central player or end effector in cell death, and many cardioprotective signaling mechanisms have been found to converge on the mitochondria and reduce cell death [1,2]. The cardioprotective strategies of ischemic preconditioning (IPC) and postconditioning (PostC) have important clinical implications. Compared to the early use of IPC, which is only practical to perform in patients undergoing coronary artery bypass grafting, PostC is more clinically relevant but there is a very narrow window for such an intervention. Although the ischemic myocardium can be salvaged via myocardial reperfusion, irreversible injury also occurs during reperfusion. The most likely cause of myocyte death during I/R injury is the disruption of cellular membranes and the loss of sarcolemmal integrity [3]. There are many components involved in cardioprotection; however, there is uncertainty as to how signaling networks interact together to confer protection. In particular, further studies are needed to explore how the signaling molecules interact and translocate to the mitochondria.

Caveolae are flask-like invaginations [4,5] that create signaling microdomains of the plasma membrane enriched with cholesterol, sphingolipids, the marker protein caveolin, and the coat protein cavin [6,7]. Caveolins have three isoforms (caveolin 1-3) and cavins consist of four isoforms (cavin 1-4). Caveolin-3 [8] and cavin-4 [9] are expressed predominantly in cardiac muscle and have been identified as important proteins involved in cardiomyopathy [10,11]. In cardiomyocytes, there are many different signaling molecules that are concentrated and organized within the caveolae, and these can mediate signal transduction [12,13]. Recent studies suggest that caveolae and caveolae-associated signaling molecules play an important role in protecting the myocardium against I/R injury [11,14]. For example, the cardiac-specific over-expression of caveolin-3 led to myocardial protection that mimicked IPC [15] and also attenuated cardiac hypertrophy [16]. Conversely, the knockout of caveolin-3 [15] or disruption of caveolae via cholesterol sequestration, abolished IPC-induced protection [17,18]. Caveolae could provide critical protection by directly sensing extracellular stress, such as ischemia or flow-induced mechanical stretch, and elicit multiple signaling pathways in order to mediate effective protection. These pathways could result in mitochondrial signaling, alteration in substrate uptake, the sensing of mechanical stretch, and/or reparation of damaged membranes.

Caveolae-Associated Cardioprotective Signaling

Multiple signaling molecules such as G-protein-coupled receptors (GPCRs), ion channels and transporters, and other important signaling molecules, are concentrated and organized within the caveolae in cardiomyocytes, producing a unique and homeostatic pH, ionic, and redox microenvironment [13,19,20]. For example, endothelial nitric oxide (NO) synthase (eNOS) [21] and NADPH oxygenase (NOX) [22] are localized in caveolae/lipid rafts. The compartmentalized generation of NO (by eNOS) and superoxide (by NOX and/or uncoupled eNOS) might have a dramatic impact on oxidative/nitrosative stress during I/R injury. Therefore, the concerted or disturbed regulation of these redox systems play important roles in physiology and disease [23]. Acute stress, as occurs with I/R, can cause a dramatic change within caveolae, thus allowing these membrane invaginations to serve as essential sensors for eliciting downstream signaling cascades.

The activation of a number of GPCRs by molecules such as adenosine, bradykinin, catecholamines, and opioids that are released by the myocardium during IPC or PostC has been found to be protective [24-26]. Recently, we found that activation of the extracellular calcium sensing receptor (CaSR), which is a GPCR that is expressed in cardiomyocytes and is predominantly localized to the caveolae,

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plays an important role in mediating IPC-induced cardioprotection [27]. Interestingly, activation of many GPCRs has been found to mimic the cardioprotective effects of IPC or PostC. However, often the effects of activating multiple GPCRs is not additive [26,28]. One possible explanation could be that activation of any of these GPCRs leads to caveolae-mediated vesicle internalization, which subsequently leads to a decrease in GPCR sensitivity in cardiomyocytes. In addition, activation of some of GPCRs may result in the activation of the same downstream signaling pathways, such as the PI3K/Akt/eNOS pathway [29]. However, studies have yet to determine whether there is sequential activation and/or interaction among different caveolae-localized receptor-mediated signaling pathways.

Caveolae-Mediated Translocation of Protective Signaling to Mitochondria

Mitochondria have been recognized as the end effector of cardioprotective interventions such as IPC and PostC [30, 31]. Caveolae-mediated endocytosis has been suggested to result in the formation of a signalasome which is thought to target mitochondria [32,33]. In our recent studies, we have found that IPC leads to the translocation of caveolin-3-associated eNOS to mitochondria, and this is associated with an increase in the S-nitrosylation (SNO) of mitochondrial proteins. Disruption of caveolae via cholesterol sequestering agents (i.e., methyl-β-cyclodextrin), abolished the mitochondrial translocation of eNOS and blocked the increase in SNO proteins and protection induced by IPC [18]. Interestingly, two populations of mitochondria, i.e., subsarcolemmal mitochondria (SSM) and interfibrillar mitochondria (IFM), are distributed in cardiomyocytes according to their subcellular localization. Given the close proximity of SSM to caveolae, it is possible that caveolae-mediated cardioprotective signaling may preferentially target to SSM rather than IFM. Since the energetics of SSM might play an important role in regulation of ionic homeostasis and thus plasma membrane integrity, the modulation of this population of mitochondria should be crucial for cardioprotection.

Substrate Uptake and Transportation

On a beat-to-beat basis, the heart has a high energetic demand that is necessary to support contractile function, ionic homeostasis, and metabolic processes. Under normal conditions, cardiomyocytes primarily use fatty acids and glucose to generate ATP via mitochondrial oxidative phosphorylation [34-36]. There is a shift in substrate preference towards glucose utilization during the development of cardiac hypertrophy, which may worsen if the hypertrophic myocardium transitions into heart failure [34,35,37]. Fatty acid and glucose uptake in the myocardium are facilitated by families of fatty acid transporters (FAT) and glucose transporters (GLUT). In cardiomyocytes, the most important FAT is fatty acid translocase, also known as CD36. This transporter is present in both plasma and microsomal fractions, and insulin does not affect the cellular distribution [38]. In mouse embryonic fibroblasts, caveolin-1 has been found to be required for CD36 localization and function at the plasma membrane [39]. However, a recent study showed normal expression and function for CD36 in caveolin-3$^{-/-}$ mouse hearts, suggesting that in cardiomyocytes, CD36-mediated fatty acid uptake is not dependent on caveolin-3 or caveolae [40].

Basal glucose uptake in cardiomyocytes is mediated by GLUT1, while increased work load or insulin stimuli leads to the plasma membrane translocation of GLUT4 and the enhancement of glucose uptake [37]. Although the uptake and oxidation of fatty acids and glucose were normal in caveolin-3$^{-/-}$ mice [40], recent studies suggest that caveolae may also play an important role as metabolic platforms [19,41]. Horikawa et al. have shown that anesthetic preconditioning is dependent on the presence of caveolae and the expression of caveolin-3 [42]. Tsutsumi et al. used an *in vivo* I/R model to test anesthetic preconditioning in wild-type, caveolin-1$^{-/-}$, and caveolin-3$^{-/-}$ mice and found that wild-type and caveolin-1$^{-/-}$ mice could be protected, while caveolin-3$^{-/-}$ mice in which caveolae are totally lost in cardiomyocytes, could not be protected. Further, they found that delayed anesthetic preconditioning appears to be associated with the specific up-regulation and co-localization of GLUT-4 with caveolin-3 [41]. Myocardial ischemia is reported to stimulate glucose uptake via GLUT-4 translocation from intracellular vesicles to the sarcolemma. Koneru et al. found that there was a significant role for the Akt/eNOS/Cav-3 signaling pathway in mediating the sarcolemmal translocation of GLUT-4 in the IPC heart, thus leading to myocardial protection [43]. In addition, the IPC-induced Akt/eNOS/Cav-3-mediated GLUT-4 translocation to the sarcolemma could be abolished with the use of a reducing agent, suggesting a potential role for redox-dependent signaling (i.e., NO-mediated protein S-nitrosylation).

Mechanical Stress Sensing and Membrane Repair

Mechanical or shear stress has been found to induce caveolae formation and the activation of extracellular signal-regulated kinase (ERK) in vascular endothelial cells [44,45], and caveolae function as a mechanotransduction sensor in the cardiovascular system [46]. Kozera et al. showed that in cardiomyocytes, caveolae provide a means of buffering changes in membrane tension [47]. A recent study from Sinha et al. found that acute mechanical stress induced by stretching or osmotic swelling led to the rapid disassembly and disappearance of caveolae, while reducing mechanical stress results in caveolae reassembly [48]. Direct evidence for the sensing of mechanical stress by caveolae comes from a recent study which showed that myotubes from muscular dystrophic patients have enhanced membrane fragility under mechanical stress in which there is an absence of functional caveolae reservoirs [48]. The mechanical stretch-induced disassembly of caveolae and redistribution of glycosphingolipids may be an important cellular adaptation to mechanical stretch [49]. Thus, during cell stretch or swelling, as occurs during I/R, caveolar membranes may serve as critical plasma membrane components that could be incorporated into the sarcolemmal surface to maintain membrane integrity.

Besides sensing mechanical stress in the plasma membrane, caveolins are also involved in the regulation of membrane repair. Mutations in caveolin-3 and the muscle repair protein dysferlin are linked to muscular dystrophy, and caveolin-3 has been found to cause the surface retention of dysferlin and regulate endocytosis of the muscle repair protein dysferlin [50]. Recent studies from Dr. Ma's group have discovered that a muscle-specific TRIM family protein (TRIM72), also named as mitsugumin 53 (MG53), interacts with caveolin-3 and dysferlin to regulate membrane repair in striated muscle [51-53]. Cao et al. found that I/R causes the down-regulation of MG53, which could be prevented by IPC [54]. In addition, MG53 deficiency increases myocardial vulnerability to I/R injury and abolishes IPC-induced protection. The cardioprotective effects of MG53 are attributable to the MG53-dependent interaction of caveolin-3 with PI3K and the subsequent activation of the reperfusion injury salvage kinase pathway [54]. In another study, Wang et al. found that ablation of MG53 prevents membrane repair and exacerbates mitochondrial dysfunction and the loss of cardiomyocytes during I/R injury [55]. Interestingly, MG53-dependent membrane repair is mediated by a cholesterol-dependent mechanism, which may also be related to the trafficking of caveolae [55].

Change of Caveolae in Aged and Diseased Hearts

Myocardial IPC represents one of the most powerful endogenous protective mechanisms against I/R injury. IPC-induced cardioprotection seems to be reduced with aging, both in experimental [56-58] and clinical studies [59,60]. Recent studies also suggest that PostC-induced cardioprotection is lost in aged animals [58,61]. Alterations to intracellular myocardial ultrastructure and signaling pathways may be responsible for this age-related decline in cardioprotection. Emerging data suggest that caveolae play important role(s) in cardioprotection [14,16,18,41], and caveolin-3$^{-/-}$ mice have been shown to develop a progressive cardiomyopathic phenotype [62]. The dissociation of caveolin from caveolae has also been found to be associated with aging and heart failure [63]. During early adulthood in mice (four months), caveolin-3$^{-/-}$ hearts display significant hypertrophy, dilation, and reduced fractional shortening. A recent study demonstrated that there is a selective decrease in the expression of caveolin-3 in murine models of heart failure, and in failing human hearts, there is a direct correlation between the levels of caveolin-3 and other markers of the heart failure phenotype [64]. Thus, a decrease or the loss of caveolin-3/caveolae has the potential to lead to a loss of cardioprotection and the development of heart disease during aging [65,66].

Therapeutic Prospective

In muscle, mutation and deficiency in the caveolin-3 gene lead to various caveolinmyopathies and one mutation in caveolin-3 has been reported to be the cause of hypertrophic cardiomyopathy. A recent study by Horikawa et al. showed that cardiac-specific over-expression of caveolin-3 via adenovirus, attenuates cardiac hypertrophy [11]. This provides a promising result for the use of caveolin-3 as a therapeutic target in the heart. In addition, an early study by Young et al. showed that perfusion with a caveolin-1 peptide from the scaffolding region, led to vascular dilation via enhanced release of endothelium-derived NO, and significantly attenuated post-I/R-induced cardiac contractile dysfunction in isolated perfused rat hearts [67]. Given our recent study suggesting that caveolae may transduce signaling via the eNOS/NO/SNO pathway in IPC hearts, it would be interesting to test whether perfusion with a caveolin-3 mimic peptide from the scaffolding region could also elicit protective effects in I/R hearts [68].

Lipid composition is important for the structure and function of caveolae. Disruption of caveolae by cholesterol-depleting agents, such as cyclodextrin, has been routinely applied in cell and animal studies. Statins, which are widely used as lipid-lowering drugs, have been also used in the prevention and treatment of coronary artery disease because of their ability to increase NO bioavailability, improve endothelial function, and enhance antioxidant and anti-inflammatory effects. A recent clinical study showed that perioperative simvastatin therapy significantly reduced myocardial injury and inflammation in patients undergoing noncoronary artery surgery by activating eNOS with an increase in Hsp90 expression and a decrease in caveolin-1 expression. Simvastatin has cardioprotective effects that are independent from its

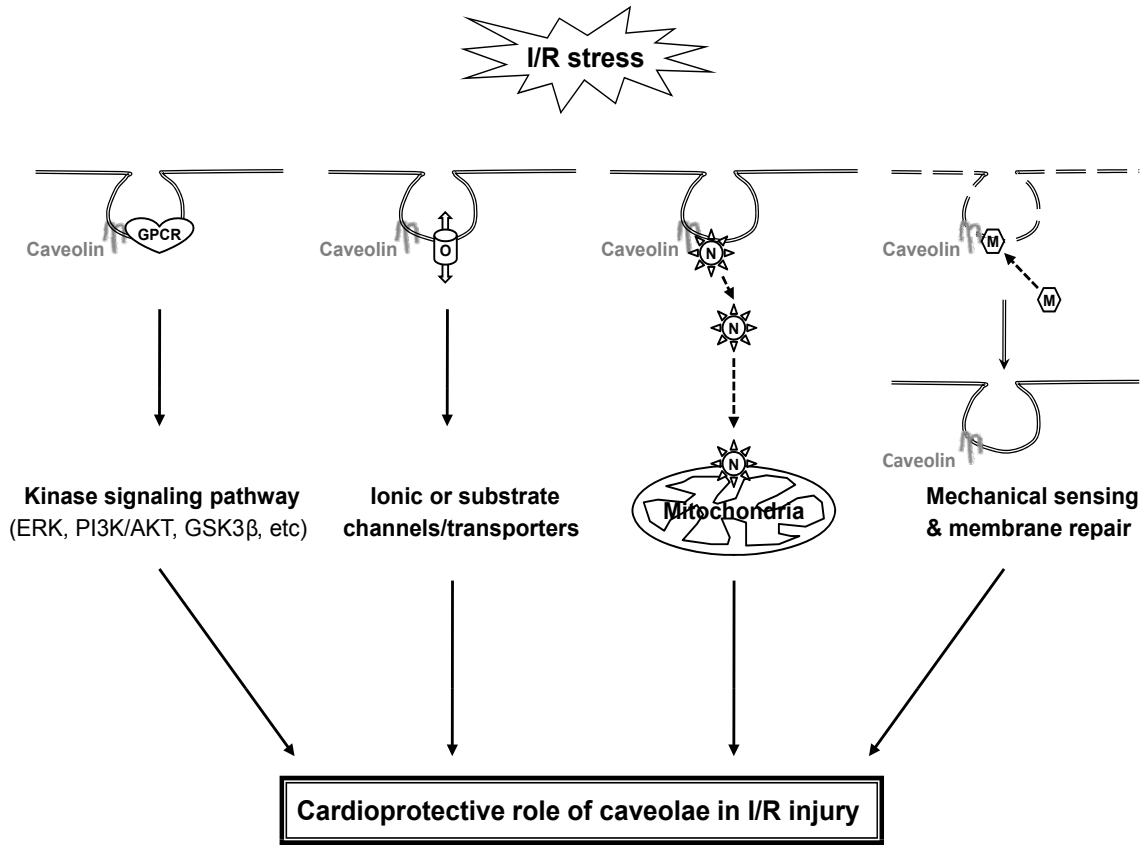

Figure 1: Cardioprotective role of caveolae in I/R injury. Caveloae can potentially sense and respond to myocardial I/R stress by (1) initiating various GPCR-coupled kinase signaling pathways; (2) changing the activities of ionic or substrate channels/transporters ("O"); (3) activating and translocating specific caveolae-associated signaling molecules ("N"), such as eNOS; and (4) sensing mechanical stress and initiating plasma membrane repair ("M").

ability to reduce lipid levels and mainly relies on changes in caveolin and caveolin-associated signaling molecules. This suggests that therapeutic interventions that seek to modify caveolae/caveolin levels may be promising for treating ischemic diseases. In addition, Oshikawa et al. showed that extracellular superoxide dismutase (ecSOD) localized at caveolae catalyzes the dismutation of superoxide to H_2O_2, which is essential for the full activation of VEGF signaling and the promotion of angiogenesis after ischemia. Thus, caveolae could also serve as a potential therapeutic target for angiogenesis-dependent cardiovascular disease [69].

Although caveolae are found in almost all mammalian cell types, endothelial cells usually show a higher level of caveolae and this reflects the physiological role of caveolae in these cell types (i.e., engage in vesicular traffic for uptake, internalization and transportation of molecules). The monolayer of endothelial cells lining vessel walls forms a size-selective and semipermeable barrier which controls the movement of fluid between the blood and interstitial tissues, thus allowing for the potential exploitation of caveolae-mediated delivery systems for cardioprotective nano-compounds and an exciting therapeutic prospective.

In conclusion, caveolin-3 and caveolae play important protective roles in the myocardium by regulating GPCR-coupled kinase signaling pathways, changing the activity of ionic or substrate channels/transporters, activating and translocating specific caveolae-associated signaling molecules, and sensing mechanical stress and initiating plasma membrane repair (Figure 1). As a result, emerging data suggest that caveolae may be an effective therapeutic target for the treatment of myocardial ischemia and caveolae-related cardiomyopathies [70].

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