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Review Article

Caveolae and Caveolin: Potential Targets for Cardioprotection

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ABSTRACT

Caveolae are sphingolipid and cholesterol rich micro-domains of the plasma membrane that coordinate and regulate varieties of signaling processes. Caveolae present in essentially all cell types of the cardiovascular system, including endothelial cells, smooth muscle cells, macrophages, cardiac myocytes, and fibroblasts. Numerous functions have been ascribed to this omega-shaped sphingolipid and cholesterol rich micro-domains.

Caveolae are receiving increasing attention as cellular organelles contributing to the pathogenesis of several structural and functional processes including cardiac hypertrophy and heart failure. At present, very little is known about the role of caveolae in cardiac function and diseases, although recent studies with caveolin knock-out mouse have shown that caveolae and caveolins play a pivotal role in various human pathobiological conditions. This review will discuss the possible role of caveolae in cardiac health and disease.

Keywords: caveolae, caveolin, heart, cardioprotection.

INTRODUCTION

The "fluid-mosaic model" suggested by Singer and Nicolson in 1972 described the membrane as a fluid bilayer with a homogeneous lipid distribution. In recent years this model has been refined as the plasma membrane, which has been shown to consist of defined lipid rich regions interspersed with more fluidic membrane regions resulting in a much more complex view of the membrane than originally hypothesized. Caveolae are subcellular structures that were first described using electron microscopy in 1953 by George Palade. Initially, these invaginations were identified as plasmalemmal vesicles. Two years later in 1955, similar structures were reported by Yamada E, in the gall bladder epithelium, and were described as caveolae intracellulares due to their cave-like, invaginated appearance [Fig-1]. Since their initial discovery, caveolae have been found in almost all cell types. Recent studies have shown that caveolar microdomains are more than lipid enriched invaginations of the plasma membrane. [1] Caveolae play an important role in physiological functions such as cell signaling, [2,3] endocytosis, calcium homeostasis, adrenergic receptor regulation, and intracellular cholesterol transport. [4-6]

Caveolins, structural proteins essential for caveolae formation, are present in three isoforms (Cav-1, Cav-2 and Cav-3). Cav-1 was the first member of the caveolin family to be identified as a phosphorylated protein. Caveolins are a family of 21- to 25-kDa integral membrane proteins that have been implicated in a variety of cellular functions. [1] Currently, three caveolin genes are known to exist. Caveolin-1 and caveolin-2 are ubiquitously expressed, while the expression of caveolin-3 is muscle specific. [7, 8]

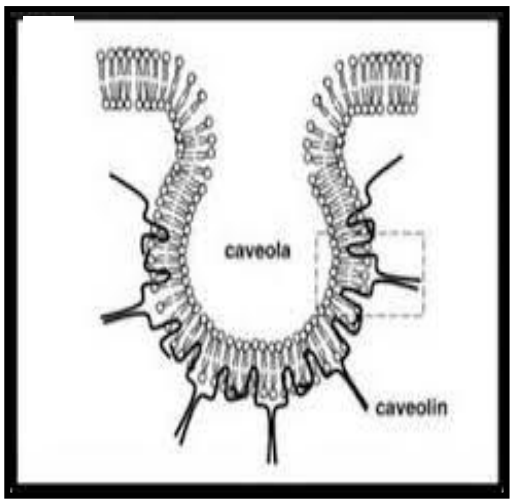

Fig 1- Diagrammatic representation of caveolae.
[from : P. L. Tuma, A. L. Hubbard. (2003) Transcytosis: Crossing cellular barrires. Physiological Reviews. 83 (3):871-932]

Caveolae and Cellular Signaling Components

A large number of GPCR (G-protein coupled receptor) have been reported to co-localize with caveolae. In case of Angiotensin I receptor, GPCR-caveolin interaction is important for receptor sorting and delivery to plasma membrane. [9] According to the caveolin signaling hypothesis, caveolae bring downstream effectors in proximity to receptors (e.g., GPCRs) for initiating receptor, tissue and cell-specific signal transduction. [10,11] These effectors are thought to reside within caveolae by direct interaction with caveolin. Palmitoylation may enhance caveolar localization of proteins. [12,13]

Among the different binding proteins of caveolin, its interaction with eNOS has been most extensively studied. [14] Binding of eNOS with caveolin inhibits enzyme activity [15] and loss of caveolin expression upregulates eNOS activity. [16] Like eNOS, caveolin is also thought to negatively regulate Adenylate Cyclase (AC) activity. Caveolin-1 and caveolin-3, but not caveolin-2 inhibits AC activity and this inhibition is AC isoforms. [17] Like eNOS, protein kinases (PKA/PKC) can also interact with caveolin-1 and inhibit its activity. [18] The PKC family of enzymes translocate to the cellular compartment in response to the external stimuli. [19] The phosphatidylinositol-3-kinase/protein kinase B (PI3K/PKB, Akt) pathway is another protein kinase system that interacts with caveolin and this interaction may regulate cell survival. For example, caveolin retains Akt in activated form (phosphorylated form) in prostate cancer, [20] presumably via interaction with caveolin scaffolding domain of caveolin and by inhibition of protein phosphatase 1 and 2A. [21] In muscle, we can also found a linear relationship between the expression of caveolin-3 and activation of PI3K/Akt pathway in the regulation of cell survival. [22] In addition, the phosphorylated form of caveolin is involved in EGF receptor transactivation, which is dependent on Src and Akt phosphorylation and for which caveolin helps integrate this signaling cascade. [23]

Receptor tyrosine kinases also have been localized to caveolae [e.g., EGF, NGF, IGF and PGDF] and their downstream effectors MAP kinases, which regulate numerous cellular processes, are also regulated by caveolin. [24,25] P42/44 MAPK localizes to caveolae and is negatively regulated by interaction with caveolin 1. [26] Overexpression of caveolin-1 also inhibits the MEK/ERK signaling pathways. [27] Consistent with this action, caveolin-1 and-3 knockout mice showed increased activation of p42/44 MAPK. [28] Ischemia reperfusion showed differential activation of p42/44 ERK and p38MAPK in cavaeolar and noncaveolar fraction, indicating differential regulation of these kinases by caveolin. [29] Certain non-receptor tyrosine kinases such as members of src family (c-Src, Fyn, lyn) are enriched in caveolae and interactions with caveolin-1 also suppress the kinases activities. [30,31] Tyrosine phosphorylation of caveolin itself makes phospho caveolin, which acts as a key site of tyrosine kinase signaling. [32]

Caveolin Knockout and Different Cardiomyopathies

The elucidation of the role of caveolae has been the topic of many investigations which were greatly enhanced

after the discovery of caveolin, the protein marker of these flask-shaped plasma membrane invaginations. The generation of mice deficient in the various caveolin genes (cav-1, cav-2 and cav-3) has provided physiological models to unravel the role of caveolins or caveolae at the whole organism level.

Caveolin-KO mice (Cav-1,-2, -3) and caveolin 1/3 double KO mice have already been developed. Although they are viable, they are fertile but display numerous phenotypes. Caveolin-1 knockout mice develop progressive cardiac hypertrophy as demonstrated by transthoracic echocardiography (TTE) and magnetic resonance imaging (MRI). [28] In contrast, caveolin-3 knockout mice develop cardiomyopathy characterized by hypertrophy, vasodilatation and reduced contractility as well. [33] Caveolin-1 and caveolin-3 double knockout mice completely lacking caveolae are deficient in all three caveolin proteins because caveolin-2 is degraded in absence of caveolin-1. The double knockout mice developed severe cardiomyopathic phenotype with cardiac hypertrophy and decreased contractility. [34] Additionally, Cav-1 KO mice exhibited myocardial hypertrophy, pulmonary hypertension and alveolar cell hyper proliferation caused by constitutive activation of p42/44 mitogen activated protein kinase and Akt. [35] Interestingly, in Cav-1-reconstituted mice, cardiac hypertrophy and pulmonary hypertension were completely rescued. [35] Again, genetic ablation of Cav-1 leads to a striking biventricular hypertrophy and to a sustained eNOS hyper-activation yielding increased systemic NO levels. [36] Furthermore, a diminished ATP content and reduced level of cyclic AMP in hearts of knockout mice was also reported. [36] Taken together, these results indicate that genetic disruption of caveolin-1 is sufficient to induce severe biventricular hypertrophy with signs of systolic and diastolic heart failure. [36]

Apart from its ability to degrade extracellular matrix proteins, matrix metalloproteinase-2 (MMP-2) was recently revealed to have targets and actions within the cardiac myocyte. MMP-2 (gelatinase A) has been localized to the thin and thick myofilaments of the cardiac sarcomere, as well as to the nucleus. [37,38] The intracellular proteins troponin I and myosin light chain-1 are proteolyzed by MMP-2 in ischemia/reperfusion injury. [37,38] The tissue inhibitors of metalloproteinase (TIMPs) control MMP activities, [39] but other mechanisms of regulation are less well elucidated. In endothelial cells, MMP-2 has been localized to the caveolae [40] yet its function there is unknown. Disruption of caveolae activates MMP-2 in fibrosarcoma cells [41] while Cav-1 overexpression in tumor cells causes decreased MMP-2 activity [42] suggesting that Cav-1 may participate in the regulation of MMP-2. Whether the role of MMP-2 activity in the heart is affected by caveolin still remains unknown. Here we present evidence that MMP-2 localizes with Cav-1 in the mouse heart, and that CSD inhibits MMP-2 activity and that hearts of mice deficient in Cav-1 have increased MMP-2 activity.

Interestingly, Cav-3 KO mice show a number of myopathic changes, consistent with a mild to moderate muscular dystrophy phenotype. However, it remains unknown whether a loss of cav-3 affects the phenotypic behavior of cardiac myocytes in vivo. Cav-3 knockout hearts display significant hypertrophy, dilation and reduced fractional shortening as revealed by gated cardiac MRI and transthoracic echocardiography. Histological analysis reveals marked cardiac myocyte hypertrophy, with accompanying cellular infiltrates and progressive interstitial/ peri-vascular fibrosis. It has also demonstrated that p42/44MAPK (ERK1/2) is hyperactivated in heart derived from caveolin-3 knockout mice, which can lead to cardiac hypertrophy. [43]

In the endoplasmic reticulum, Cav-3 initiates the biogenesis of caveolae organelles by forming homooligomers and hetero-oligomers with Cav-1. [44] At the

plasmalemma, Cav-3 interacts with dystrophin and its associated glycoproteins. [45,46] Cav-3 and dystrophin competitively bind to the same site of β-dystroglycan, suggesting that Cav-3 may regulate the membrane recruitment of dystrophin and the assembly of the dystrophin glycoprotein complex (DGC). [47] At the cell surface, Cav-3 colocalizes also with signaling molecules such as Gi2α, Gβ γ, c-Src, other Src kinases as well as nitric oxide synthases (neuronal and inducible NOS), indicating that muscle caveolae might be involved in the modulation of these signaling processes. [48,49] In addition, Cav-3 plays a role in the regulation of energy metabolism of muscle cells as it is required for the cell membrane targeting of phosphofructokinase, an enzyme that catalyzes a rate-limiting reaction in glycolysis. [50]

In vitro studies have shown that Cav-3 plays a critical role in myoblast cell differentiation and survival and in myotube formation. [51] The relevance of Cav-3 in muscle physiology was further confirmed by the findings that mutations in the CAV3 gene result in distinct neuromuscular and cardiac disorders, such as limb girdle muscular dystrophy (LGMD) 1-C, idiopathic persistent elevation of serum creatine kinase (hyperCKemia), inherited rippling muscle disease (RMD), distal myopathy and familial hypertrophic cardiomyopathy (HCM). [52-54]

CAVEOLAE AND CARDIAC ION CHANNELS

Modulation of ion channel activity plays a critical role in regulating cardiovascular function. Recently, it has become apparent that the regulation of channel function is not the only means of controlling excitability, the trafficking and localization of ion channels with signaling molecules also play a significant role. Most cells in the cardiovascular system express multiple channel types (e.g., voltage-gated Na^+, K^+ and Ca^{2+} channels) and even multiple isoforms of a particular channel, with each channel uniquely contributing to excitability. [55,56] Voltage gated Na^+ channels are responsible for the initial depolarization of the cardiac sarcolemma, to permit the opening of voltage-gated L-type Ca^{2+} channels, resulting in Ca^{2+} influx and contraction. Membrane repolarization is controlled by K^+ channels. Therefore, altering the number of channels and/or their function can have significant impact on both resting membrane potential and the cardiac action potential wave form. Defects in either of these processes can have life-threatening implications. [55,56]

In several cell types, including smooth muscle and endothelial cells, mediators of calcium signaling, such as Ca^{2+}-ATPase, inositol-triphosphate receptor (IP3R), Ca^{2+} pumps and L-type Ca^{2+} channels, large conductance Ca^{2+} activated K^+ channel, calmodulin and transient receptor potential (TRP) channels, localize in cholestetrol-rich membrane domains. Such localization suggest that membrane raft and/or caveolae have a role in calcium handling and Ca^{2+} entry that control excitation-contraction of heart muscle. [57,58] TRP channels, in particular TRPC1, -3 and -4 are enriched in caveolae and caveolin-1 regulates the plasma membrane localization and function of TRP channels. [59] Current evidence indicates that caveolae regulate calcium entry and depletion of cholesterol by methyl-β-cyclodextrin reduces colocalization of caveolin-1 and TRPC1 and redistribution of TRPC1, thus preventing Ca^{2+}influx. [60] Moreover, Na^+ pump, Na/K-ATPase, contains two caveolin binding motifs and resides in caveolae in a number of cells, including smooth muscle cells and cardiomyocytes, thereby helping to maintain Na^+ gradient. [61] Voltage gated K^+ channels are also localized in caveolae and play an important role to maintaining cellular excitability. In fibroblast, the Kv 1.5 subunit colocalizes with caveolin-1, Kv 2.5 localizes with membrane raft and depletion of cholesterol with MβCD redistributes and alters the function of K^+ channel. [62] These findings imply that alteration of caveolae and/or caveolin by any disease or drug

treatments can shift the localization of the channels, thereby altering cellular excitability and functional activity.

CAVEOLAE AND CARDIOVASCULAR DISEASE

Normal heart physiology and vascular function is frequently disrupted and thereby gives rise to a multitude of pathological states. In recent years, many researchers have found that both caveolins and caveolae play a role in the development of various human diseases, including coronary heart disease, hypertension, stroke and nervous system disorders. [63]

There is a vast literature about the roles of caveolae and caveolin in the regulation of many cellular processes in cultured cells and many investigators considered them as an essential platform of signaling molecules. However, in the past few years, development of animal models and usage of genetically altered mice have been instrumental in deciphering their physiological functions in vivo. Transgenic over expression of caveolin-1 or caveolin-3 in mice or targeted disruption of each of the caveolin gene locus in mice (Cav-1, Cav-2 and Cav-3 genes) has provided significant insight into the roles of caveolin and caveolae. [64] The potential role of caveolin in cardiovascular physiology has become apparent by the discovery of cavelin-1 and caveolin-3 KO mice and double knockout mice, which have cardiomyopathic phenotype. Caveolin-1 KO mice show complete ablation of the presence of the caveolae, cellular organelle, in the endothelium and fat. Similarly, caveolin-3 KO mice lack caveolae in cells that normally express this protein such as skeletal muscle, heart and diaphragm. Heart tissue is made up of different types of cells. Differentiated cardiomyocytes surrounded by a network of cardiac fibroblasts and endothelial cells and less abundant vascular smooth muscle cells. There is also a controversy regarding expression of caveolin isoforms in the heart muscle. It is well known that cardiac myocytes express caveolin-3 and other cell types in the heart express caveolin-1 and caveolin-2. But recent studies provided the evidence of the existence of caveolin-1 in cardiomyocytes. [65]

Caveolae and their coat proteins, caveolins (Cav), have diverse effects on endothelial function, nitric oxide synthesis regulation, signal transduction, cholesterol metabolism, and apoptosis. Animal studies in Cav knockout mice demonstrate the vital role of these structural proteins on endothelial and vascular function. Genetic studies have proposed that beside neoplasia, Cavs may play a role in the development of atherosclerosis, cardiomyopathy, long QT syndrome, pulmonary fibrosis, and muscular dystrophy. Ongoing research is needed to clarify the diagnostic and prognostic role of these novel proteins and to determine how the effects of Cavs can translate into clinical medicine. [66]

Caveolin and Atherosclerosis

Atherosclerosis is a disease of the blood vessel characterized by the development of an arterial occlusion containing lipid and cellular deposits. Caveolae and caveolins are believed to play an important role in the regulation of cellular signaling and transport of molecules among others. Experimental evidence indicates that caveolae and caveolins have the possibility to influencing atherogenesis in many ways. Caveolin-1 is a cholesterol-binding protein that can transport cholesterol from the endoplasmic reticulum (ER) to the plasma membrane. The major receptors for high-density lipoprotein, SR-B1, and a scavenger receptor for modified forms of LDL, CD36, can also reside in and signal in caveolae-type microdomains. [67] In addition, oxidized LDL can extract caveolae cholesterol, unlocalize eNOS, and impair NO release. [68] Conversely, blockade of HMG CoA reductase with statin-based drugs reduces caveolin levels and promotes eNOS activation. [69] This concept has been

validated in apolipoprotein E-deficient ($ApoE^{-/-}$) mice where statin treatment decreases caveolin-1 expression and promotes NOS function in vivo. [70] However, to date, there are no data showing changes in caveolin-1 levels in atherosclerotic lesions from humans. [64]

To verify, if caveolin-1 influenced lesion progression in mice, Lisanti and his coworkers crossbred caveolin-$1^{-/-}$ mice with $ApoE^{-/-}$ mice that develop atheromas. Interestingly, the loss of caveolin-1 in the $ApoE^{-/-}$ mice resulted in a proatherogenic lipid profile, similar to that seen in $CD36^{-/-}$ mice bred to an ApoE background. [71,72] Surprisingly, despite a pro-atherogenic lipid profile, the loss of caveolin-1 reduced lesion burden by 80%, suggesting caveolin-1 regulated LDL-mediated vascular dysfunction, inflammation, and lesion progression. The authors suggested this may be caused by a decrease in stability of the scavenger receptor for oxidized or modified LDL, CD36 in macrophages, and an increase in endothelium-derived NO production, which would reduce vascular inflammation. These remarkable findings unequivocally support the importance of caveolin-1/caveolae in the pathogenesis of atherosclerosis. [64]

But the role of Cav expression in atherosclerotic disease is poorly understood and remains controversial. Interestingly, there is emerging evidence between low Cav-1 levels and the vulnerable plaque, which could potentially identify Cav-1 as a novel plaque biomarker. [66]

Endothelial dysfunction is crucial in the initiation of atherosclerosis, which is associated with a lack of nitric oxide. The endothelial NO synthase (eNOS) is responsible for constitutive synthesis of NO and inhibited by caveolin-1 (Cav1). Loss of Cav1 increased vascular lesion by enhancing neointimal proliferation. The combined loss of Cav1 and eNOS, compared to $Cav1^{-/-}$, lowered intima formation, suggesting an increasing effect of eNOS in the absence of Cav1 on vascular lesion. [73]

Global deletion of CAV1 in mice results in insulin resistance and increases in atherogenic plasma lipids and cholesterol, but protects from diet-induced obesity and atherosclerosis. . In this study the cellular dynamics of intestinal Cav1 were visualized in zebrafish and the metabolic contributions of CAV1 were determined with mice lacking CAV1 in intestinal epithelial cells. [74]

Caveolin and Cardiac Hypertrophy

The heart responds to multiple forms of stress with an adaptive hypertrophic increase in cardiac mass. Under prolonged stress, the heart undergoes an apparent irreversible change, resulting in dilation, diminished performance, and ultimate failure. Given that cardiac failure is the most common result of insufficiency of myocardium, it is not surprising that cardiomyocyte hypertrophy is the dominant cellular response to virtually all forms of hemodynamic overload. [75] However, long-term adaptive/compensatory hypertrophy is associated with progressive ventricular dilation. As a consequence of cardiac enlargement and wall thinning, stress on the wall also increases, despite constant intracavitary pressure. This mathematical increase in wall stress generates its own hemodynamic stress on the heart, further stimulating overloaded hypertrophy signaling pathway and thereby altering the balance from cell growth response to cell death. Once these processes have progressed to this stage (decompensation, loss of cardiac myocytes), irreversible functional deterioration develops, which leads to heart failure and, ultimately, death. [76,77]

Over-expression of caveolin-3 in neonatal cardiac myocytes decreases the ability of the adrenergic agonist phenylephrine or endothelin-1 to increase cell size. [74] A similar kind of effect is seen in cardiac myoblasts (H9C2) in which cav-3 reduces angiotensin II–promoted hypertrophy. [78] Other studies indicate that cardiac hypertrophy results in decreased expression of cav-3 and hypertrophy is enhanced in caveolin-1 KO and caveolin-

1/3 double KO mice. [79,80] Down regulation of growth signals are the most likely cause of expressed caveolin induced inhibition of cardiomyocyte gowth. Cav-1 and -3 KO mice show hyperactivation of p42/44 MAPK [81] and upregulation of eNOS activity and nitrosative stres [82, 65] By contrast, increased caveolin expression down regulates activity of those entities. [83,84] Chronic myocardial hypoxia increases eNOS expression while decreasing the expression of cav-3, consistent with the idea that the expression and activity of eNOS is dependent on caveolin. [85] A recent finding indicate that caveolin-1 overexpression reduces hypertrophy by inhibiting autophagy pathway. [86] Alterations in caveolin expression almost certainly change the ability of the hypertrophied heart to respond to a variety of physiologic and pharmacologic agonists/ stimulus. [65]

Caveolin and Myocardial Ischemia

Myocardial infarction (i.e., heart attack) is the irreversible death (necrosis) of heart muscle secondary to prolonged lack of oxygen supply (ischemia). Ischemic heart disease is leading cause of death and disability worldwide. Precondition (PC) is the phenomenon whereby brief episodes of ischemia and reperfusion render the heart resistant to ischemic injury from a subsequent ischemic insult. Thus, ischemic PC is a protective and adaptive mechanism produced by short periods of ischemic stress rendering the heart more protected against another similar or greater stress. Early preconditioning depends on adenosine, opioids and to a lesser degree, on bradykinin and prostaglandins, released during ischemia. This molecule activate G-protein coupled receptor, initiates activation of K_{ATP} channel and generate oxygen free radicals, and stimulate a series of protein kinases, which include protein kinase C, tyrosine kinase and members of MAP kinase family. Late preconditioning is triggered by a similar sequence of events, but in addition essentially depends on newly synthesized proteins, which comprise iNOS, COX-2, manganese superoxide dismutase and possibly heat shock proteins. The final mechanism of PC is still not very clear. However, evidence is rapidly accumulating about the involvement of caveolin or caveolae in cardioprotection against myocardial ischemia and ischemia/reperfusion injury. [87]

Ischemia/reperfusion injury activates p42/44 and p38MAPK, redistributes caveolin-3 and downregulates expression of caveolin-1. [87] Disruption of caveolae using MβCD eliminates the ability of ischemia and pharmacological preconditioning to protect the cardiac myocyte from injury. [88] This is also supported by the decreased ability of Cav-1 KO mice to undergo pharmacological preconditioning. [87] Emerging evidences indicate that caveolin-1 (Cav-1), and caveolin-3 (Cav-3) both are essential for the protective effects of conditioning against myocardial I/R injury. [89] Recent investigations also showed that pro-survival signaling components translocate and/or interact with caveolin in ischemia/reperfusion heart and render the heart less abundance to pro-survival signal and induces myocardial injury. Similarly, in preconditioned heart death signaling components translocates and/or interact with caveolin in preconditioned heart and rendering the heart less exposed to death signaling components and more abundant to pro-survival signaling components [90] [Fig-2]. Although detail mechanism of action of caveolin is not very clear, but evidence indicates that proteasomes and histone modification play a very important role in the interaction between caveolin and signaling components. [91,92] We found that Cav-1 KO mouse abolished the acetylation of histone (H3 and H4) and increased the methylation of histone in the preconditioned heart. The increased histone methylation was significantly correlated with an increased level of histone methyltranferase G9a protein and increased the level of histone decaetylase (HDAC) activity. Recent investigation also shown that Cav-3 knockdown cells showed increased cell death and higher level of apoptotic proteins

(cleaved caspase-3 and cytochrome c) with suppressed mitochondrial function in response to simulated ischemia and I/R, whereas Cav-3 overexpressed cells were protected and had preserved mitochondrial function. [93] In the heart, autophagy may be a major regulator of protection from ischemic stress. It was found that Cav-3 knockdown cells have a decreased expression of autophagy markers [beclin-1, light chain (LC3-II)] after simulated ischemia and ischemia-reperfusion (I/R) compared with WT, whereas overexpressed cells showed increased expression. [93] However, overall observation indicates that caveolin plays a pivotal role in cardioprotection against ischemic injury.

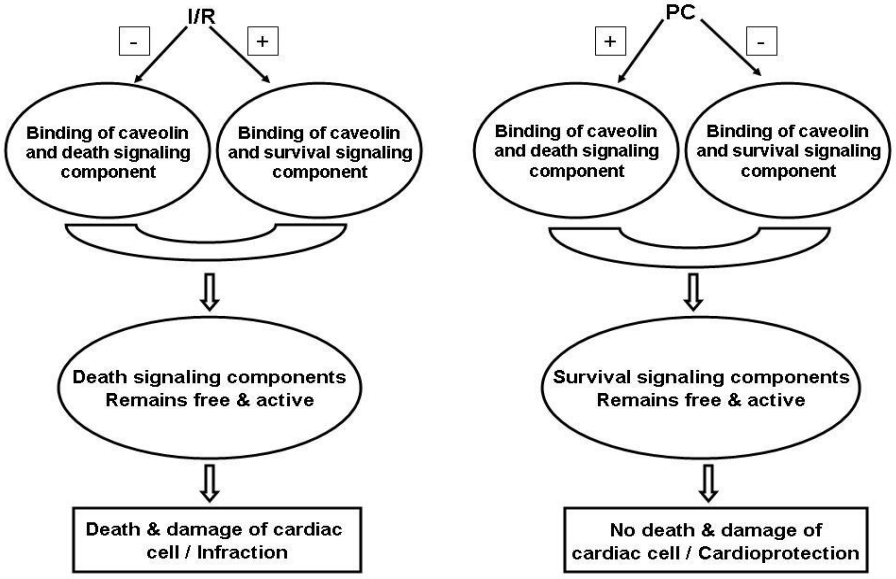

Fig -2: The role of caveolae in the ischemic preconditioning of the heart. In I/R heart, survival signaling components remain bound (+) with caveolin, whereas there was reduced association (-) of death signaling components with caveolin. These unbound death signaling components induces reperfusion injury in the heart. In PC heart, death signaling components remain bound (+) with caveolin, whereas there was reduced association (-) of survival signaling components with caveolin. These unbound anti-death/survival signaling components induced cardioprotection.

CONCLUSION

Caveolae and caveolins are comparatively new players in a relatively saturated field of cardiovascular diseases and are undoubtedly regulating various aspects of cardiovascular system. Clearly loss of caveolin-1 has profound effect on the eNOS pathway, indicating the importance of this interaction, whereas the loss of caveolin-3 impacts NOS as well as MAPK activation and histone acetylation. Transgenic over expression of caveolin-1 or caveolin-3 in mice or targeted disruption of each of the caveolin gene locus in mice (Cav-1, Cav-2 and Cav-3 genes) has provided significant insight into the roles of caveolin and caveolae. The potential role of caveolin in cardiovascular physiology has become apparent by the discovery of cavelin-1 and caveolin-3 KO mice and double knockout mice, which have cardiomyopathic phenotype. Although detail mechanisms of actions are not very clear, experimental evidences demonstrate the predominant role of caveolin in cardiac hypertrophy, atherosclerosis, ischemic injury and different myocardial functions. Recent investigations are disentangling the complex processes of caveolin regulated signaling systems in the myocardium and developing novel approaches, aimed at counteracting cardiomyocyte apoptosis in heart failure and/or cardiovascular diseases.

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