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Two Novel Approaches Providing Cardiac Protection Against Oxidative Stress

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1. Introduction

Coronary artery disease is the highest contributor to morbidity and premature death in the developed world (Nabel, 2003; Fuster et al., 1992; Melo et al., 2004). Cardiac function is compromised in patients that survive an initial ischemic event and this progressive myocardial impairment leads to heart failure (Liu et al., 2007; Sugamura and Keaney, 2011; Jessup and Brozena, 2003). High levels of reactive oxygen species (ROS) contribute to the process of disease progression in both myocardial ischemia and in models of heart failure. ROS play a role in short term responses (stunning and arrhythmias) as well as long term responses (infarction) to ischemia with reperfusion. The primary source of ROS in myocardial ischemia is from mitochondria of cardiac cells with additional ROS arising from neutrophils that infiltrate ischemic regions (Sugamura and Keaney, 2011). There have been promising preclinical studies employing some antioxidant enzymes but there are no currently accepted clinical applications of these enzymes for myocardial ischemia (Downey, 1990; Zweier et al., 1987, Otani et al., 1986; Papaharalambus and Griendling, 2007; Vivekananthan et al., 2003). It is likely that the responses in the ischemic heart are more complicated than was initially realized and other antioxidant based strategies have to be developed. Our work has focused on two protective agents that act to prevent the detrimental effects of oxidative stress in the ischemic heart. The first cardio-protectant is methionine methionine sulfoxide reductase A (MsrA), a member of the Msr family of enzymes. The other major enzyme in the Msr family is MsrB and these two enzymes differ in their substrate stereo-specificity. The Msr family of enzymes can protect cells in two ways: 1) by repairing oxidative damage to critical methionine (Met) residues in proteins which have been oxidized to methionine sulfoxide (met(o)), and 2) by functioning as part of an ROS scavenger system in which Met residues in proteins function as catalytic antioxidants. MsrA has been studied in most detail and shown to protect bacterial and animal cells against oxidative damage (for review see Weissbach et al., 2005). The studies with MsrA led to investigations with the drug sulindac, a known non-steroidal anti-

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inflammatory drug (NSAID), that is a substrate for the Msr system (Etienne et al. 2003; Brunell et al. 2011). Sulindac protects the heart against ischemic infarction through a newly described activity as a pharmacological preconditioning agent (Moench et al., 2009).

2. Antioxidant therapies and oxidative stress in heart disease

ROS normally produced as a by-product of the electron transport chain are now considered to be a major factor in aging and age related diseases (Bokov et al., 2004). In the heart high levels of ROS have been implicated in both ischemic damage and in the progression of heart failure (Giordano, 2005). Preclinical studies for ischemic heart disease employing antioxidants although still at an early stage have shown some promise (Sugamura and Keaney, 2011; Bolli et al., 2004; Cannon, 2005). For example heme oxygenase -1 (HO-1) based gene therapy has been proposed as a therapeutic strategy for ischemic heart disease because the enzyme has a clear antioxidant capacity (Liu et al., 2007). In addition, the products of heme metabolism, carbon monoxide and bilirubin have been reported to possess cyto-protective properties (Poss and Tonegawa, 1997; Stocker et al., 1987). Cardiac expression of HO-1 increased Akt phosphorylation and decreased infarct size in a mouse model of ischemia/reperfusion. Knockdown of the bilirubin producing enzyme biliverdin reductase increases apoptosis of cardiac cells subjected to hypoxia /re-oxygenation and decreases Akt phosphorylation. Thus the protection afforded by HO-1 involves activation of Akt that is dependent upon biliverdin reductase (Pachori et al., 2007).

Other antioxidant enzymes that have shown potential for protection against ischemic damage include extracellular superoxide dismutase (EC-SOD-1), thioredoxin (Trx), and glutathione peroxidase (GSHPx) (Agrawal et al., 2004; Yoshida et al., 1996; Turoczi et al., 2003; Maulik et al., 1999). Gene transfer of EC-SOD-1 by direct intra myocardial injection using an AAV vector resulted in high level cardio-protection in rats at 7 days following ischemia and reperfusion injury (Agrawal et al., 2004). Using the rat working heart model of transient global ischemia it has been shown that thioredoxin is substantially decreased, whereas preconditioning by non-lethal ischemia elicited up-regulation of Trx expression and induced tolerance against severe ischemic stress (Turoczi et al., 2003). Likewise Trx-1 overexpressing mice were found to have reduced myocardial infarct size after a prolonged ischemia episode (Turoczi et al., 2003). Glutathione peroxidase (GSHPx) knockout mice have been shown to be more susceptible to ischemic damage than wild type mice, whereas GSHPx overexpressing mice are protected against myocardial ischemic damage (Maulik et al., 1999).

In models of heart failure the contribution of ROS has been demonstrated to contribute to hypertrophic adaptations and to apoptosis (Li et al., 2002; Kwon et al., 2003; Giordano, 2005). Cardiac hypertrophy can be either a physiological adaptation or part of the pathology that ultimately progresses to heart failure (Giordano, 2005). ROS signaling has been implicated in hypertrophic growth associated activation of MAPKs (Sabri et al., 2003; Ghosh et al., 2003). For example, inhibition of ROS by chemical antioxidants prevents A-II induced hypertrophy (Nakamura et al., 1998; Delbosc et al., 2002). ROS induced alterations in transcription factor activation has been reported in cardiac hypertrophy and several studies point to a role for ROS in the induced chromatin remodeling in the failing heart (Giordano,

2005). ASK-1 provides a link between oxidative stress and hypertrophy since following activation by ROS, Ask1 induces activation of p38-MAPK and JNK causing apoptosis (Izumiya et al., 2003). The apoptotic process is central to heart failure and the effect of ROS on apoptosis is dependent upon the levels of ROS produced (Kwon et al., 2003). It is clear that high levels of ROS will elicit apoptosis via JNK and p38-MAPKs, whereas low levels of ROS can function as signaling molecules and help to protect cells under certain physiological conditions, as is the case with ischemic preconditioning discussed below (Kwon et al., 2003; Das, 2001; Hool, 2006; Murry et al., 1986; Yellon and Downey, 2002; Bolli, 2000).

3. MsrA and cellular protection

Of the amino acids in proteins that can be oxidized by ROS, Met is one of the most sensitive, being converted to methionine sulfoxide (Met(o)) (Weissbach et al., 2005). Since the sulfur in Met(o) has a chiral center this chemical oxidation yields a mixture of the R and S epimers, Met-R-(o) and Met-S-(o), as shown in Figure 1.
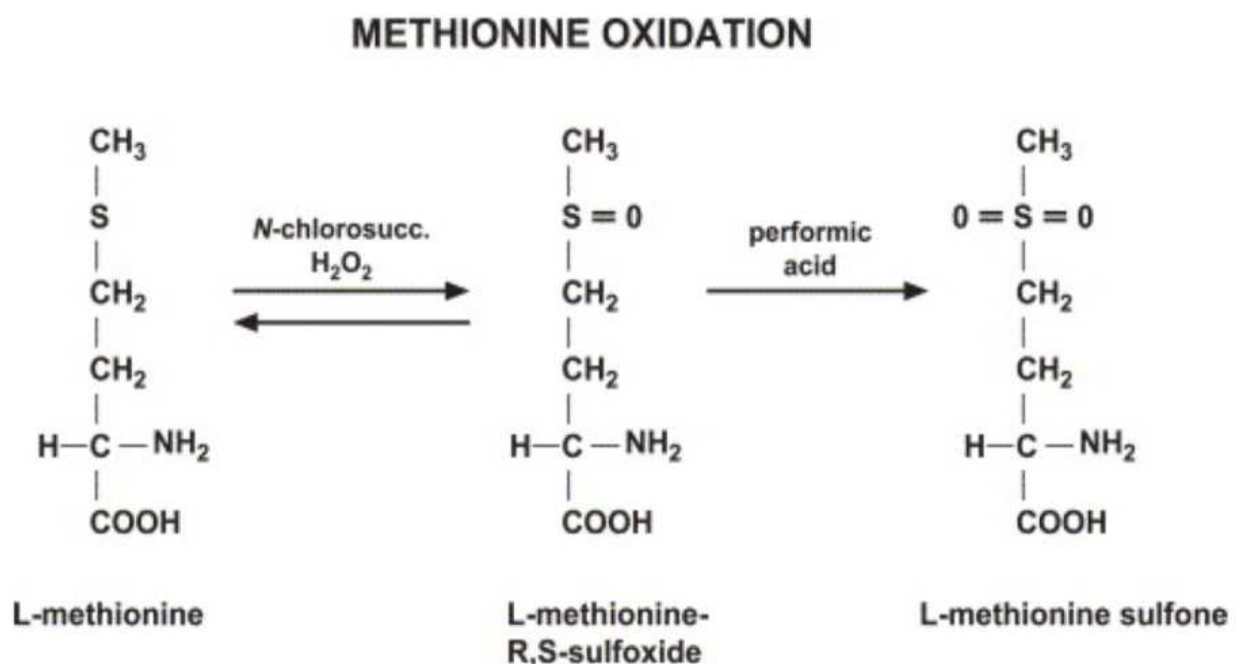
METHIONINE OXIDATION

Fig. 1. Products of methionine oxidation.

Further oxidation of Met(o), leads to the formation of methionine sulfone, which has been detected in proteins at very low levels and its significance is not known. As also shown in Figure 1 Met(o) in proteins can be reduced back to Met by the Msr enzymes. The two main members are MsrA and MsrB, which reduce the S epimer and R epimer of Met(o), respectively. It is now known that there is one msrA gene in mammalian cells and three msrB genes, the latter referred to as MsrB1, 2 and 3 (Vougier et al., 2003; Kim and Gladyshev, 2004; Hansel et al., 2005).

Although MsrA was first discovered more than 30 years ago in studies on protein synthesis in bacteria (Brot et al.,1981), its important role in protecting cells against oxidative damage only

became apparent in the early 1990's after the MsrA gene was cloned from both Escherichia coli and bovine liver (Rahman et al., 1992; Moskovitz et al., 1996). When MsrA was knocked out in E. coli the organism grew normally, but was extremely sensitive to oxidizing agents (Moskovitz et al., 1996, St. John et al., 2001). Since then there have been several studies demonstrating that over-expressing MsrA in animal cells can protect them against oxidative damage (Moskovitz et al., 1998; Kantorow et al., 2004; Yermolaieva et al., 2000) and lead to extended life span in both flies and yeast (Ruan et al., 2002, Koc et al., 2004) . As one example in cells in culture, over-expression of MsrA by transfection of PC12 cells with an adenovirus vector encoding MsrA resulted in a greater tolerance for oxidative stress following hypoxia with re-oxygenation (Yermolaieva et al., 2004). MsrA overexpressing cells showed significantly lower levels of ROS and apoptosis than cells infected with no virus or control plain virus. In Drosophila, overexpression of MsrA was protective against oxidative stress. When the MsrA transgene was over-expressed the flies were found to be more resistant to paraquat induced oxidative stress and when the MsrA was predominantly expressed in the nervous system there was a dramatic increase in lifespan (Ruan et al., 2002) (Figure 2).
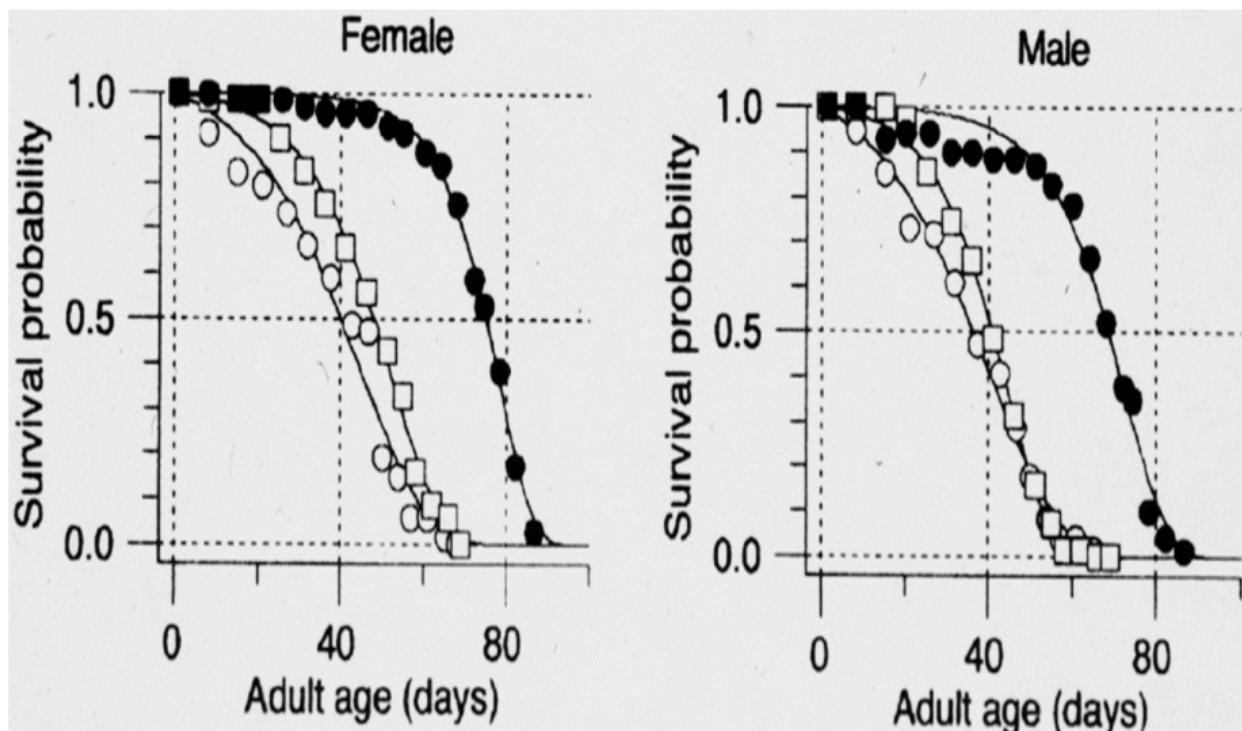

Fig. 2. Extension of life span of flies by neuronal expression of MsrA. □——□ and O-O, control flies; ●——● MsrA overexpressing flies. From Ruan et al., 2001.

To determine the effect of MsrA in protecting against hypoxia/re-oxygenation damage in cardiac cells we transduced primary rat cardiac myocytes with an MsrA encoding adenovirus (Prentice et al., 2008). In cells over-expressing MsrA, apoptotic cell death resulting from hypoxia/re-oxygenation was decreased by greater than 45% relative to cells expressing control virus (Figure 3).

The protection of cardiac myocytes in culture against hypoxia/re-oxygenation stress by MsrA over-expression points to MsrA as a potential therapeutic agent for treatment of ischemic heart disease (Prentice et al., 2008).
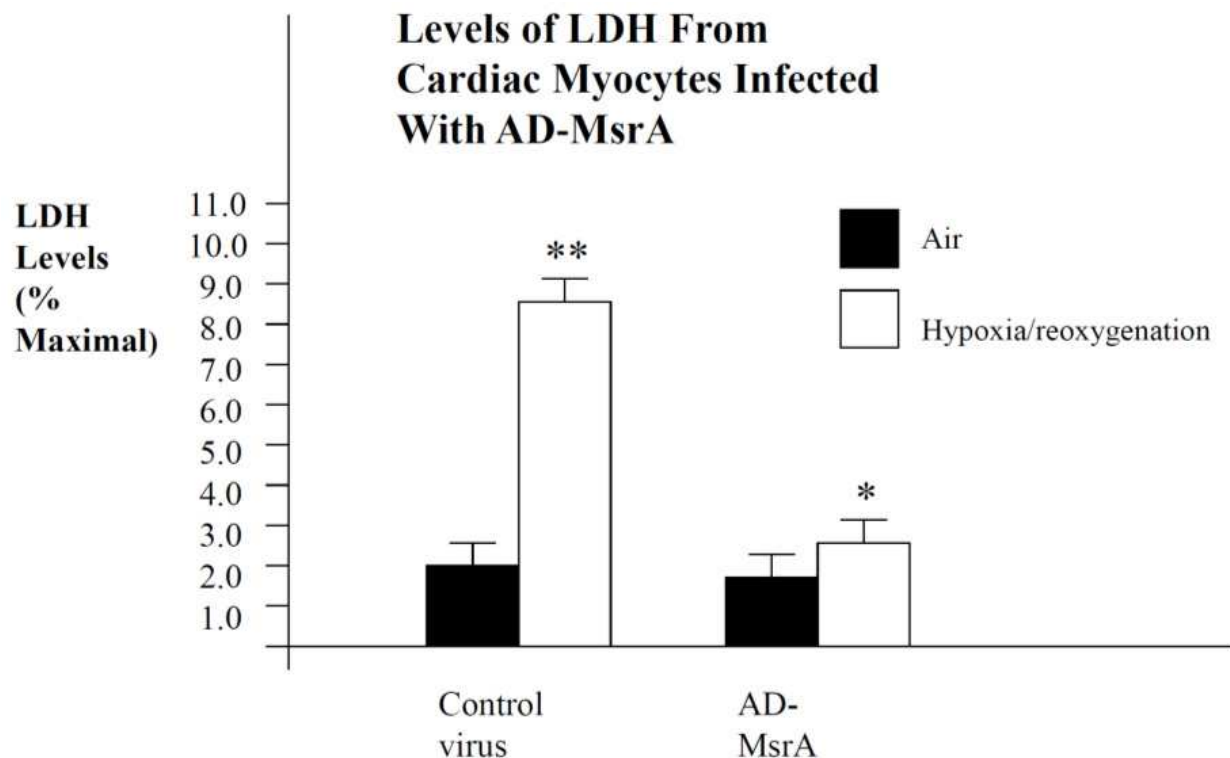
Fig. 3. Protection of cardiac myocytes following hypoxia / reoxygenation by sulindac as measured by levels of LDH released. **p<0.01 vs air control virus (N=6). *p<0.01 vs hypoxia/reoxygenation control virus (N=6). From Prentice et al. 2008

In contrast, knocking out MsrA makes mammalian cells more sensitive to oxidative stress. MsrA and MsrB knockout in lens and retinal cells make these cells more sensitive to oxidation (Marchetti et al., 2006; Kantorow et al., 2004). There have been reports on MsrA knockout mice in which it is clear that these animals are very sensitive to increased oxygen tension, although there is conflicting data on their life span and the presence of a neurological defect (Moskovitz et al., 2001, Salmon et al., 2009). The MsrA knockout mice also have been reported to contain increased brain dopamine levels at 6 and 12 months of age perhaps because of enhanced dopamine synthesis, but at 16 months the mice showed reduced dopamine levels compared to younger animals (Oien et al., 2008). Experiments addressing physiological alterations in the heart resulting from a loss of MsrA have been carried out using the MsrA-/- knock-out mouse model (Nan et al., 2010). Under normal non-stressed conditions cellular contractility and cardiac function are not altered in the MsrA-/- mice. However when cardiac cells are stressed with high stimulation frequencies (2Hz) or with hydrogen peroxide a significant modulation in cardiac contractility is seen (Figure 4).

There were corresponding changes in calcium transients in MsrA-/- cardiac myocytes treated with 2 Hz stimulation or with hydrogen peroxide. EM analysis also showed significant swelling of the mitochondria in MsrA-/-mouse hearts and protein oxidation levels in MsrA-/- mouse hearts were higher than those of wild type controls (Nan et al., 2010). Similar morphological changes in mitochondria have previously been reported in

diseased hearts either from dilated cardiomyopathy or from myocardial ischemia and such ultrastructural changes have been associated with aging and senescence (Trillo et al., 1978; Schaper et al., 1991; Scholz et al., 1994; Terman et al., 2004) . This study indicates that there is a serious defect in mitochondrial function in the hearts of MsrA-/- mice resulting in compromised contractility and cellular dysfunction, especially under stress (Nan et al., 2010).

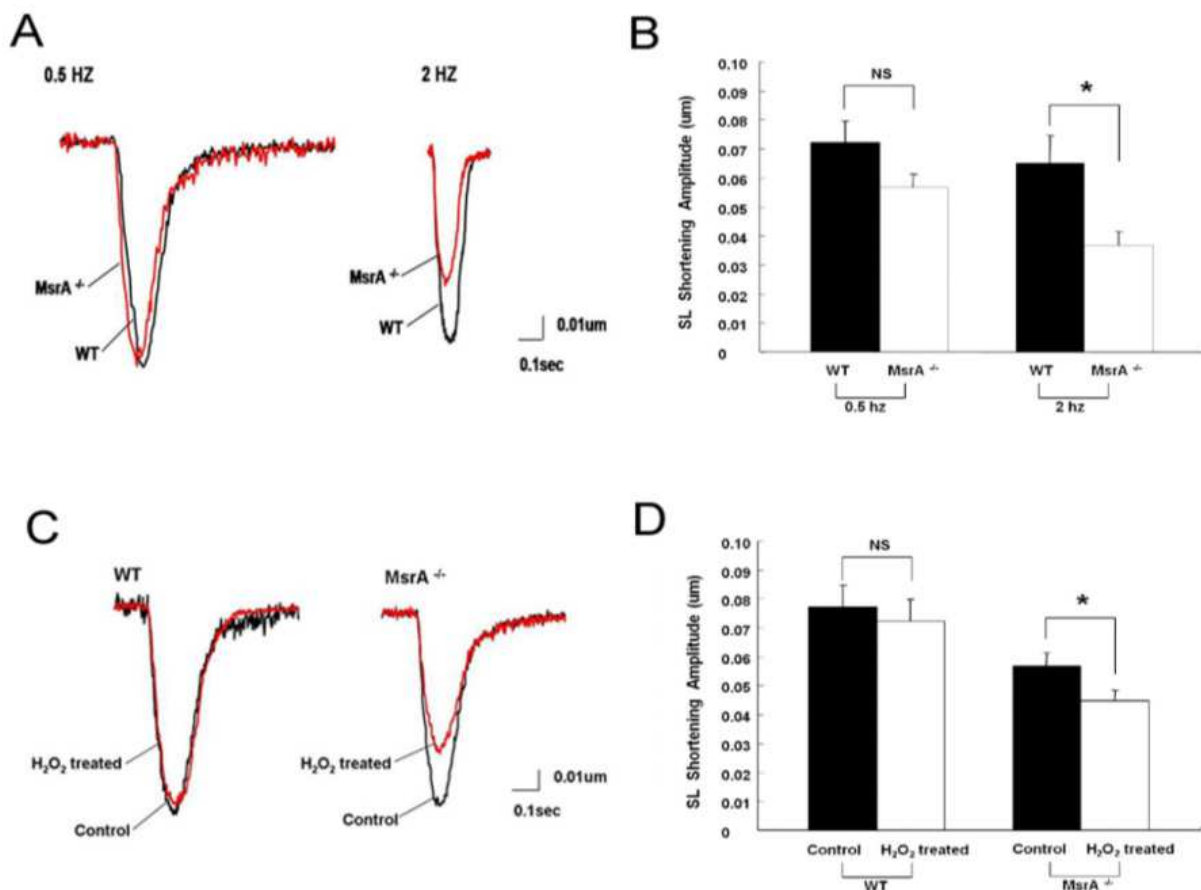Fig. 4. MsrA knockout (MsrA -/-) mice show decreased contractility when stressed by high frequency (2Hz) or with hydrogen peroxide treatment. (a) Raw traces of sarcomere contraction under 0.5 Hz or 2 Hz stimulation. (b) Shortening amplitude with 0.5Hz and 2 Hz. (c) Raw traces of sarcomere contraction with or without H2O2 treatment. (d) Shortening amplitude in cardiomycytes with or without H2O2 treatment. Data are presented as mean+/- SD and obtained from 25-30 cells (3 mice per group); *p<0.05. From Nan et al.,2010

Previous studies had demonstrated that approximately 75% of MsrA was targeted to the cytosol and 25% to the mitochondria (Kim et al., 2010; Vougier et al., 2003). A recent study by Zhao et al., (2011) examined the role of MsrA in different cellular compartments and assessed whether the enzyme would protect against ischemia reperfusion damage in the Langendorff heart. The investigators employed transgenic mice that overexpressed MsrA either in the myocardium or in the cytosol. A surprising finding was that mitochondrial targeted MsrA was not protective in the Langendorff model against ischemia/reperfusion. By contrast the cytoplasmic form of MsrA was protective, but the effect was dependent on myristoylation of the enzymes. It was proposed that myristoylation may facilitate targeting of MsrA to its protein targets to elicit myocardial protection.

4. Dual function of the Msr system

It was initially thought that the main role of the Msr system was to repair oxidative damage to proteins in which critical met residues were oxidized to met(o). There has been ample evidence that this is an important function of the Msr system. Once again most of the studies have been done with MsrA. There are now a long list of proteins and peptides whose activities are altered by Met oxidation in vitro (Brot and Weissbach, 2000) and many examples of how the activity can be restored in part by MsrA. One of the first examples was the oxidation of Met 358 in alpha one proteinase inhibitor. This enzyme, which may play a role in emphysema, loses its protease inhibitor activity when this Met is oxidized and the activity can be restored by MsrA (Abrams et al., 1981). More recently, oxidation of met residues in proteins has been reported to cause a major change in function of a number of proteins. As examples, in a shaker ShC/B voltage gated potassium channel, when a key methionine residue in the inactivation ball is oxidized, the channel activation is slowed down, but this process is reversed by MsrA (Ciorba et al., 1997). A methionine in the C terminus of calmodulin is selectively oxidized by hydrogen peroxide (Yao et al., 1996). The extent of oxidative modification was found to correlate with loss of CaM dependent activation of the plasma membrane Ca-ATPase. The protein calcium/calmodulin (Ca2+ CaM) dependent protein kinase II (CamKII) links increases in intracellular calcium to activation of ion channels, transcriptional responses and cell fate decisions. A recent study analyzing the role of CaMKII in heart demonstrated that CamKII is a common signaling point for increased apoptosis regulated by ROS, catecholamine signaling and angiotensin-II (Ang-II) (Erickson et al., 2008). MsrA was found to be essential for reversing CaMKII methionine oxidation in the ischemic heart in vivo.

However, Levine et al. (1996), in their studies on glutamine synthetase, first introduced the important concept that the Msr system could be part of a ROS scavenger mechanism. In this mechanism, Met residues in proteins, even when not at an active site, can be oxidized to Met(o) and in the process destroy a ROS molecule. The Msr system could then regenerate the Met which could once again be oxidized by an ROS molecule. Thus, the Met residues in proteins could function as catalytic anti-oxidants dependent on the Msr system. There are now several cell culture studies to support this mechanism. In PC12 cells over-expression of MsrA lowers the level of ROS in the cells and in lens and retinal cells knocking out of MsrA leads to higher ROS levels (Yermolaieva et al., 2004; Marchetti et al., 2006).

5. Sulindac is a substrate for the Msr enzymes

If Met residues in proteins could function as catalytic anti-oxidants based on the Msr system it seemed reasonable that other substrates of the Msr enzymes might function in cells as catalytic anti-oxidants. One such compound that was shown to be a substrate for MsrA was sulindac, a known NSAID (Duggan et al., 1977). The structure of sulindac and its metabolites is shown in Figure 5. Sulindac is a prodrug that must be reduced to sulindac sulfide which is the active NSAID. Since sulindac is also a mixture of the R and S epimers the metabolism of both epimers has been recently elucidated as shown in Figure 5 (Brunell et al., 2011).
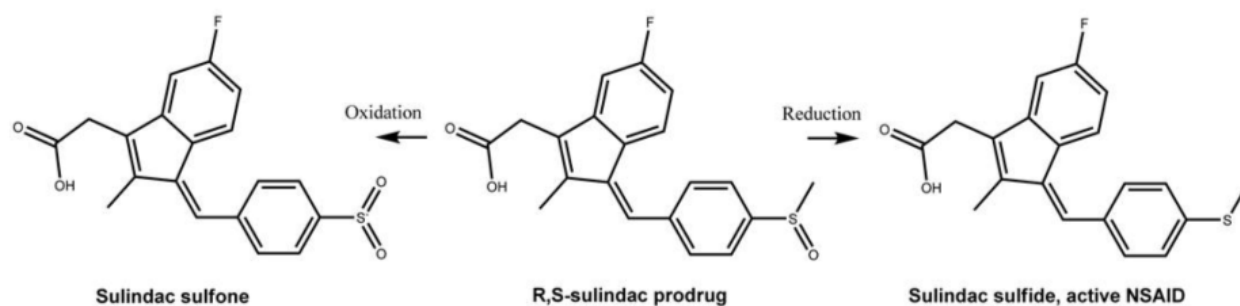
Fig. 5. Metabolism of the sulindac epimers. The R and S epimers of sulindac can be oxidized to sulindac sulfone and reduced to sulindac sulfide. From Brunell et al. 2011.

The reduction of the S epimer is catalyzed by MsrA and as seen in Figure 6, the R epimer is reduced by an enzyme in liver that has the properties of MsrB (Brunell et al., 2011). Sulindac can also induce the P450 system and be oxidized by the P450 system to sulindac sulfone (Ciolino et al., 2008; Brunell et al., 2011). Sulindac sulfone is not an NSAID and is not a substrate for the Msr system. It seemed reasonable to see whether sulindac might function as a catalytic anti-oxidant and protect cells against oxidative damage. In our preliminary experiments several normal cells were not protected by sulindac after exposure to oxidative stress, but normal lung cells were (Marchetti et al., 2009). An unexpected finding was that under similar conditions colon and lung cancer cell lines, that were pretreated with sulindac, showed enhanced killing of these cells when exposed to oxidative stress. The protective effect of sulindac with normal lung cells and the enhanced killing with the cancer cell lines was not due to the NSAID activity of sulindac or did it involve the Msr system since sulindac sulfone gave a similar effect as sulindac (Marchetti et al., 2009). As will be shown below, using cardiac cells, the protection seen against oxidative damage by sulindac is by an ischemic preconditioning mechanism (Moench et al., 2009).

6. Sulindac causes cardiac protection by ischemic preconditioning

Pharmacological preconditioning has been reported to occur in response to certain drugs that mimic the effects of ischemic preconditioning, a process known to elicit protective responses against myocardial stunning and infarction. Ischemic preconditioning has been reported to elicit an early phase of protection from 0-2 hours after the initial stimulus as well as a late phase of preconditioning from 1 -7 days after ischemia (Kuzuya et al., 1993; Marber et al., 1993; Bolli, 2000). A number of pharmacological agents can induce preconditioning include cytokines, opioids, adenosine, nitric oxide donors and bradykinin although these agents may differ in their capacity to protect against infarction, stunning or both infarction and stunning (Bolli, 2000).

The mechanisms of early preconditioning have been shown to involve NO activation of soluble guanylyl cyclase (GC), activation of PKG and opening of mitochondrial ATP dependent potassium channels (K-ATP channels) (Costa et al., 2008). Subsequent generation of ROS from the mitochondrion results in activation of PKC (Costa et al., 2008; Baines et al., 1997; Tritto et al., 1997). The mediation events of early preconditioning have been shown to

involve inhibition of the formation of the mitochondrial permeability transition pore, and in some cases, such as with protection by adenosine, this mediation involves PKC activation and PKG activation (Costa et al., 2008).

Late preconditioning is triggered through the action of NO as well as through ROS release (Bolli, 2001; Bolli et al., 1997). PKC epsilon translocates to the membrane fraction which is then followed by activation of the MAPK signaling cascade (Xuan et al., 2007). Downstream events include phosphorylation of STAT1/3 and activation of STAT dependent genes which include the COX-2 gene. Other events that mediate late preconditioning include NO release (through a PKG dependent mechanisms and opening of mitochondrial K(ATP) channels (Bernardo et al., 1999; Ockaili et al., 1999). It has been reported that the NO that mediates late preconditioning is derived from inducible NOS (iNOS). Some of the components involved in ischemic preconditioning are summarized in Figure 6.
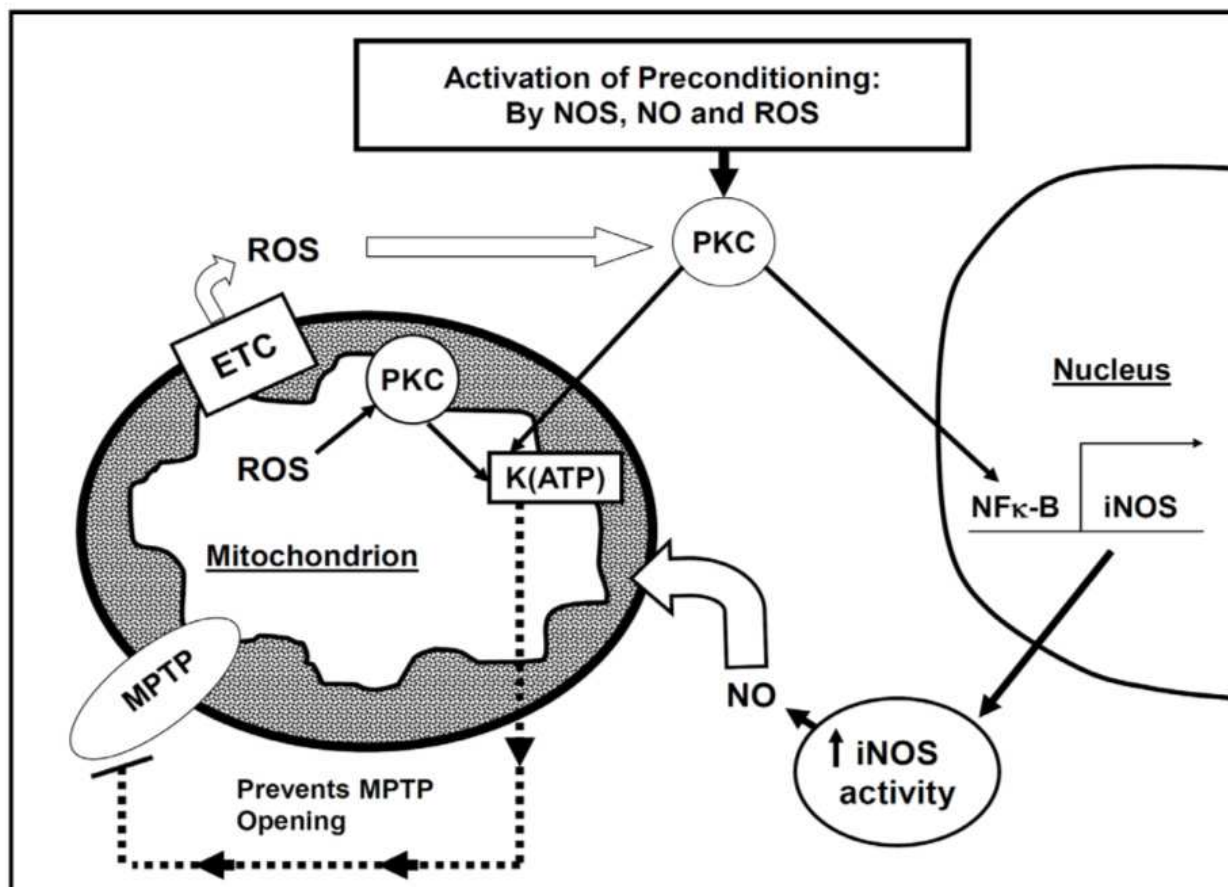

Fig. 6. Overview of mechanisms of preconditioning involving PKC, iNOS and mitochondrial pro-survival events.

In investigating the role of sulindac as a protective agent we examined the effect of sulindac treatment on neonatal rat cardiac myocytes subjected to hypoxia and re-oxygenation and in an ex vivo Langendorff model of myocardial ischemia (Moench et al., 2009). We demonstrated that sulindac (<100uM) afforded high level protection of cardiac myocytes subjected to hypoxia and re-oxygenation (Figure 7).
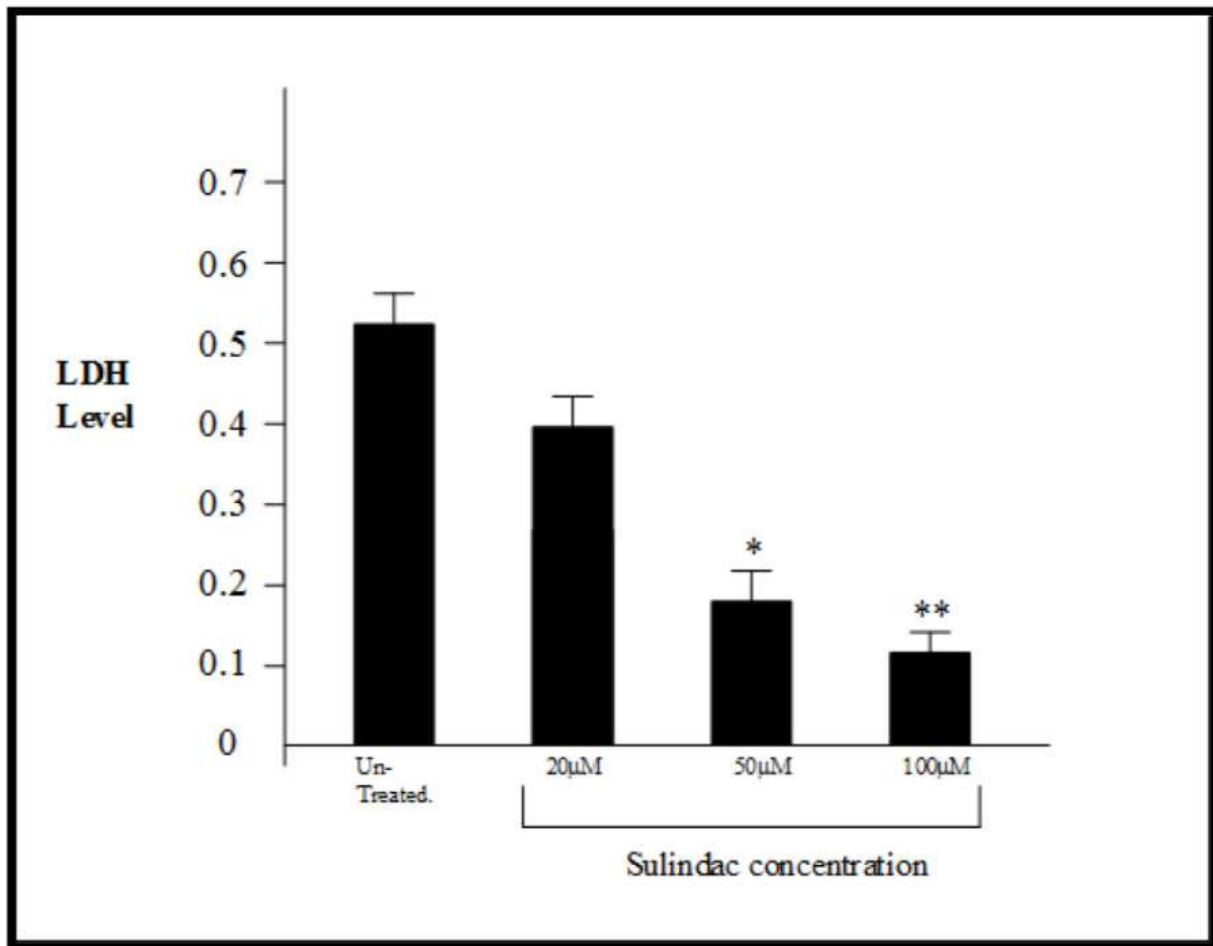
Fig. 7. Sulindac protects cardiac myocytes against oxidative damage. Cardiac myocytes were exposed to hypoxia for 24 h and reoxygenation for 20 h to elicit oxidative stress in the presence or absence of sulindac. Lactate dehydrogenase (LDH) levels (shown as absorbance units) were measured in the media as an index of cell death and levels were compared to those for untreated myocytes (*,P<0.05 vs. no drug; n=6, **, p<0.01 vs. no drug; n=6). From Moench et al., 2009.

In the Langendorff experiments rats were fed sulindac for 2 days prior to removal of the heart which was then subjected to 45 minutes of ischemia followed by 2 hours of reperfusion with oxygenated buffer (Figure 8). Sulindac was highly protective against myocardial ischemia through mechanisms that did not involve Cox inhibition or its anti-inflammatory capacity.

As an example, the NSAID ibuprofen was not capable of protecting against no flow ischemia in the Langendorff model. Furthermore the oxidized form of sulindac, sulindac sulfone, which as mentioned, is not an NSAID was found to give significant protection against ischemic damage. Through the use of a PKC inhibitor and a ROS scavenging agent we have demonstrated that sulindac protects the heart from ischemic stress by acting as a pharmacological preconditioning agent. PKC is known to mediate preconditioning either by ischemia or by pharmacological agents and in our studies daily administration of the PKC blocker chelerytherine removed the protection provided by sulindac (Figure 8). The
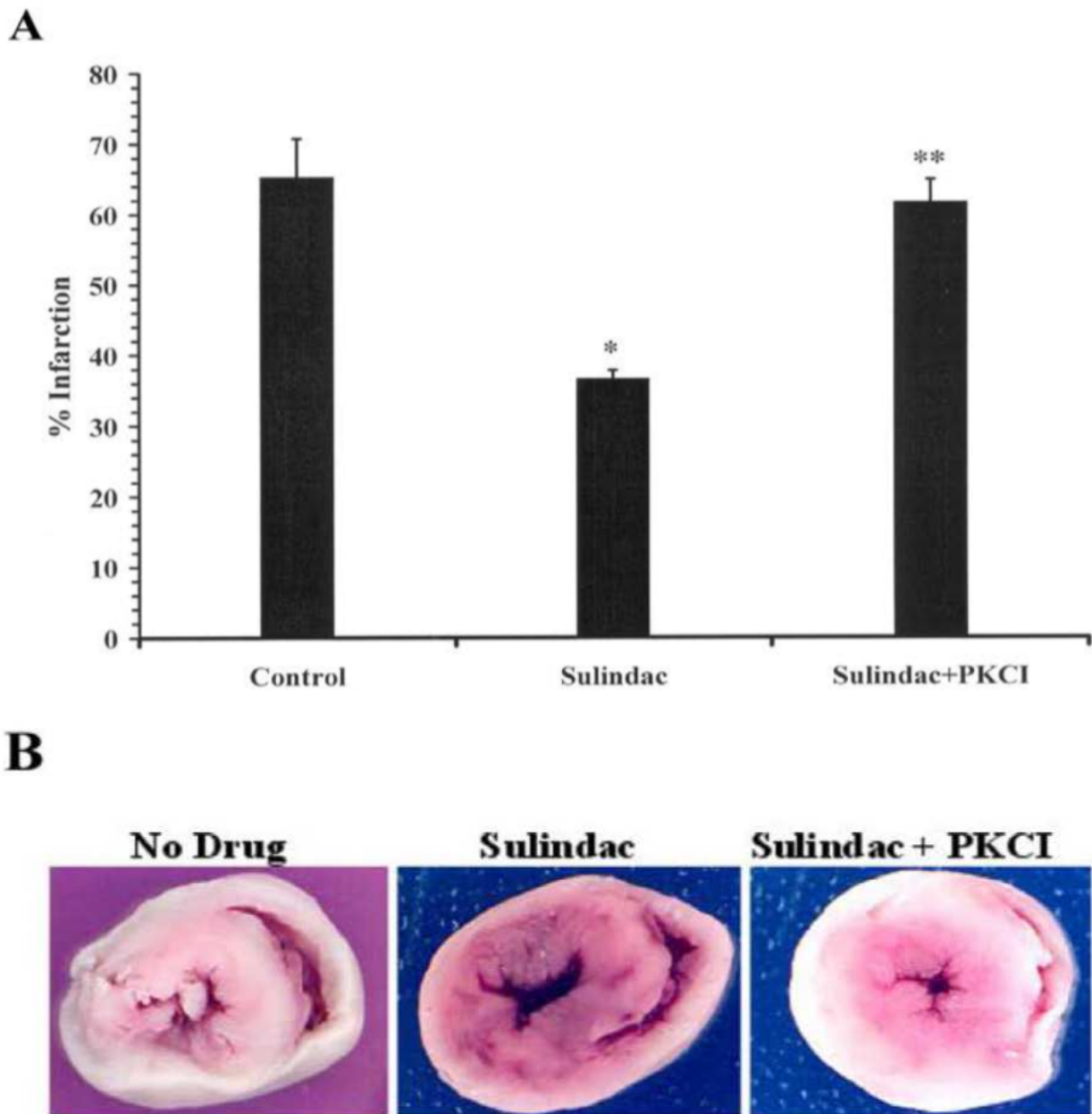
Fig. 8. Effect of feeding sulindac on infarct size after ischemia and reperfusion as measured by TTC staining. Where indicated the PKC inhibitor chelerythrine was administered to the animals. (A) Graph represents percent of heart that was infarcted (*, P<0.01 compared to no-drug control; n=4, **., P<0.01 compared to sulindac treated hearts; n=4). (B) Representative sections from langendorff hearts subjected to 45 min ischemia and 2h reperfusion showing viable tissue (red) and infarcted tissue (white). From Moench et al. 2009.

mechanism of sulindac protection appear to involve the following steps: 1) ROS increase as a trigger for subsequent signaling, 2) signaling through PKC, 3) induction of expression of downstream gene products including iNOS and Hsp27. Ongoing experiments are addressing more specifically the PKC isoforms involved in the protective action of sulindac, in addition to identifying mitochondrial signals that may contribute to the pro-survival response.

As noted above, a remarkable property of sulindac is its ability to kill cancer cells in the presence of an oxidant while being able to protect certain normal cells through pharmacological preconditioning (Marchetti et al., 2009; Moench et al., 2009). It is notable that a similar phenomenon has recently been reported for the PDE-5 inhibitor sildenafil (Das et al., 2010). This drug was found to enhance the doxorubicin induced killing of prostate cancer cells while also protecting cardiac cells from doxorubicin induced cardiomyopathy. The mechanisms of doxorubicin induced killing of cancer cells involved enhanced generation of ROS (Das et al., 2010). It will be important in future studies to determine the ways by which sulindac and sildenafil are capable of modifying the effects of increased ROS in cardiac cells leading to cell survival while also sensitizing cancer cells to oxidative stress resulting in killing of these cells.

7. Final thoughts

Antioxidant based approaches have already shown potential as strategies for the treatment of heart disease and interventions that increase intracellular MsrA have been protective in cardiac cells either through preventing an increase in ROS levels or through modifying important protein targets. Future therapies that are likely to be successful using the MsrA system may need to focus on activation of endogenous MsrA through applying pharmacological activators of MsrA identified from library screening procedures. A recent study by Minniti and colleagues (Minniti et al., 2009) noted that the MsrA promoter is activated by FOXO3A (De Luca et al., 2010). On the basis of this finding a potentially powerful strategy for increasing MsrA expression would involve transfer of FOXO3A protein into cells as a highly permeable TAT-FOXO3A-fusion protein which in turn would translocate to the nucleus and activate the MsrA gene. A simpler and more direct avenue for increasing MsrA levels would be to transfer a TAT-MsrA fusion protein directly into cells.

Regarding sulindac, although there has been serious concern that NSAIDs cause cardiac damage, here we demonstrate that at the concentrations used sulindac can, in fact, afford cardiac protection through preconditioning mechanisms. This is very likely due to the fact that a substantially lower dose is needed for preconditioning than was previously employed for anti-inflammatory applications. Future approaches based on the preconditioning properties of sulindac may involve metabolites or derivatives that are not NSAIDs and do not inhibit COX 1 or COX2. One such metabolite, sulindac sulfone, has been shown to be lacking in NSAID activity but has the cardiac protectant activity (Moench et al., 2009). As there is a very significant need clinically for effective cardioprotective agents our recent studies on cell culture and in vivo models showing high level cardiac protection by MsrA and by sulindac may point to the future application of these agents as important therapeutic breakthroughs for heart disease.

8. Acknowledgements

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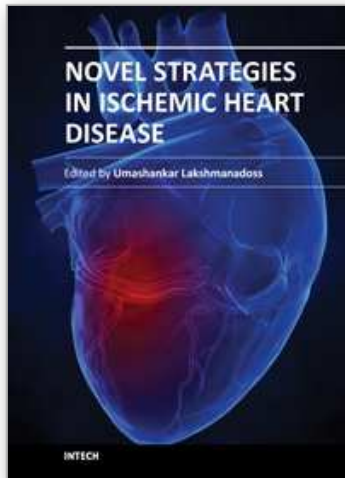
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Howard Prentice and Herbert Weissbach (2012). Two Novel Approaches Providing Cardiac Protection Against Oxidative Stress, Novel Strategies in Ischemic Heart Disease, Dr. Umashankar Lakshmanadoss (Ed.), ISBN: 978-953-51-0184-0, InTech, Available from: http://www.intechopen.com/books/novel-strategies-in-ischemic-heart-disease/two-novel-approaches-providing-cardiac-protection-against-oxidative-stress-

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