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A brief overview of cardioprotective signaling

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Abstract

Cardioprotection is defined as the intrinsic ability of cardiac tissue to withstand challenges like ischemia-reperfusion and different metabolic stresses. Initially observed through ischemic preconditioning, the scope of cardioprotection has expanded to include other inducers of cardioprotective signaling like hypoxia, temperature fluctuations, and many pharmacological agents, suggesting the existence of shared signaling pathways and protective cascades. So far, intracellular signaling factors contributing to cardioprotection include protein kinases, the reperfusion injury salvage kinase (RISK) pathway, the Survivor Activating Factor Enhancement (SAFE) pathway, hypoxia-inducible factor-1α (HIF1α), microRNAs, Connexin 43, and many others. These factors play roles in activating downstream signaling elements and protective genes, enhancing mitochondrial function, and regulating protein expression and cytosolic functions to confer cardioprotection. SUR2A, a regulatory subunit of sarcolemmal ATP-sensitive K^+ (K_{ATP}) channels, autophagy and mitochondria are highlighted as crucial end-effectors, with mechanisms like regulation of the mitochondrial permeability transition pore and activation of K_{ATP} channels being pivotal for cardioprotection. Despite advances in understanding these pathways, many aspects of cardioprotection remain to be better understood. It is a particular challenge to further explore therapeutic potentials and, finally, develop clinically viable strategies for cardiac protection.

Key words: cardioprotection, heart, ischemia, reperfusion, conditioning

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Introduction

Current therapies against cardiac diseases associated with myocardial ischemia are based on restitution of myocardial blood flow and decrease in myocardial metabolic demand. However, it is recognized that therapy for these diseases/conditions warrants further improvement. One promising therapeutic strategy could be based on cardioprotection (1, 2). Cardioprotection is defined as the intrinsic ability of cardiac tissue to withstand challenges like ischemia-reperfusion and different metabolic stresses. This phenomenon has been vigorously studied and a lot has been learned about the underlying mechanisms. Originally, cardioprotection was observed for the first time when brief episodes of ischemia-reperfusion improved the outcome of long-term ischemia-reperfusion challenge (1). Numerous subsequent studies revealed that cardioprotection can be induced by diverse procedures and pharmacological agents and that several signaling elements and factors contribute to this phenomenon (2, 3).

Inducers of cardioprotection

Cardioprotection can be triggered by a range of procedures, methods and substances. The first described cardioprotective procedure was termed ischemic preconditioning. This involves subjecting the heart to brief cycles of ischemia-reperfusion before prolonged ischemia, which has been shown to significantly decrease the size of myocardial infarction induced by prolonged ischemia (1). On the other hand, brief periods of ischemia-reperfusion after the prolonged insult have also been shown to be cardioprotective and they were denoted as postconditioning. More recently, remote preconditioning and postconditioning were also demonstrated, and that is when ischemia-reperfusion episodes occur at a distant non-cardiac site, which has been also shown to elicit cardioprotective effects (4). In addition, exposure to different levels of hypoxia and alterations in oxygen tension have been shown to induce cardioprotection (5-8). Temperature fluctuations, including both hyper- and hypothermia, have also been suggested as inducers of cardioprotection (9, 10). Furthermore, various compounds such as adenosine, nitric oxide, isosteviol, nicotinamide, and growth factors, among others, have been found to confer cardioprotection (11-15). Inducers of cardioprotection are summarized in Table I.

The high number of methods and compounds inducing cardioprotection would suggest that many inducers share the same signaling pathway, and/or that there are multiple cardioprotective signaling cascades.

Table I Inducers of cardioprotection

Tabela I Induktori kardioprotekcije

Inducer	**Description**
Ischemic Preconditioning	Subjecting the heart to brief cycles of ischemia-reperfusion before prolonged ischemia significantly decreases the size of myocardial infarction (1).
Postconditioning	Brief periods of ischemia-reperfusion after prolonged ischemia are shown to be cardioprotective (4).
Remote Preconditioning and Postconditioning	Ischemia-reperfusion episodes occurring at a distant non-cardiac site, eliciting cardioprotective effects (4).
Hypoxia and Oxygen Tension Alterations	Exposure to different levels of hypoxia and changes in oxygen tension, inducing cardioprotection (5-8).
Temperature Fluctuations	Both hyperthermia and hypothermia have been suggested as inducers of cardioprotection (9, 10).
Various Compounds	Compounds such as adenosine, nitric oxide, isosteviol, nicotinamide, and growth factors, among others, have been found to confer cardioprotection when administered externally (11-15).

Intracellular signaling of cardioprotection

So far, many different intracellular signaling factors have been suggested to contribute to cardioprotection. However, there are still no definitive answers regarding intricate interactions and temporal dynamics between different signaling elements and pathways. Several signaling molecules are widely recognized as mediators of cardioprotection.

Protein Kinases: Protein kinase C (PKC) represents one of the earliest identified components of cardioprotective signaling, with many cardioprotective agents activating this pathway. While some PKC isoforms promote cardioprotection, others may exert opposing effects. Activation of pertussis-sensitive G protein-coupled receptors triggers a cascade involving PKC, leading to the phosphorylation and activation of various targets implicated in cardioprotection (16). Additionally, protein kinase A (PKA) and AMP-activated protein kinase (AMPK) have been suggested to mediate cardioprotection (8, 17, 18). It has been shown that preconditioning activates AMPK, which, in turn, regulates the trafficking and activity of ATP-sensitive K^+ (K_{ATP}) channels to confer cardioprotection (17). Similarly, cardioprotection afforded by 15%

oxygen is mediated by AMPK (8). The roles of p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases 1/2 (ERK1/2), and protein kinase G (PKG) have also been delineated in cardioprotection (19-21).

The reperfusion injury salvage kinase (RISK) pathway, comprising phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) and MEK1-ERK1/2 cascades, is recognized as a distinct signaling entity implicated in cardioprotection. This pathway is activated during reperfusion and is associated with the transactivation of the epidermal growth factor receptor, ultimately inhibiting mitochondrial permeability transition pore opening (22). However, controversies exist regarding the necessity of certain components, such as Glycogen synthase kinase-3 beta (GSK3β), in mediating cardioprotection induced by preconditioning and postconditioning (22-24).

The Survivor Activating Factor Enhancement (SAFE) pathway has emerged as another cardioprotective signaling cascade, involving cytokines and transcription factors. Key among these factors is STAT3, whose activation has been implicated in both preconditioning and postconditioning cardioprotection (25). However, the precise roles of cytosolic and mitochondrial STAT3 in mediating cardioprotection are yet to be fully understood (26).

Hypoxia-inducible factor-1α (HIF1α) has been linked to cardioprotection. HIF-1α is an oxygen-sensitive transcription factor that mediates adaptive metabolic responses to hypoxia. It has been demonstrated that HIF-1α improves mitochondrial function, decreases cellular oxidative stress, activates cardioprotective signaling pathways and downstream protective genes, and interacts with noncoding RNAs (27).

Various microRNAs have been implicated in cardioprotection, modulating the expression of cardioprotective proteins. However, the precise mechanisms by which these microRNAs confer cardioprotection require further investigation (28).

Connexin 43 (Cx43) has been implicated in cardioprotection, with phosphorylation of sarcolemmal Cx43 and its translocation into mitochondria associated with ischemic preconditioning. Interaction with mitochondrial K_{ATP} channels and regulation of mitochondrial function further underscore its role in cardioprotection (29).

Aldehyde dehydrogenase 2, targeted by PKCε, has been identified as a mediator of cardioprotection, activated by agents like isoflurane and remote postconditioning (30).

Regulation of protein expression plays a role in cardioprotection, with various proteins implicated in preconditioning and hibernation-induced cardioprotection. These include inducible nitric oxide synthase, superoxide dismutase, aldose reductase, and heme oxygenase, among others (31).

Sirtuins are a family of NAD+-dependent deacetylases that are involved in resistance to metabolic stress and mitochondrial biogenesis. It has been suggested that sirtuin 1 promotes autophagic flux in cardiomyocytes to maintain mitochondrial homeostasis and confer cardioprotection (32).

Intracellular signaling factors involved in cardioprotection are summarized in Table II.

Table II Intracellular signalling factors mediating cardioprotection

Tabela II Unutarćelijski faktori signalizacije koji posreduju u kardioprotekciji

Signaling Factor	**Description**
Protein Kinase C (PKC)	An early component of cardioprotective signaling, activated by G protein-coupled receptors (16).
Protein Kinase A (PKA)	Implicated in cardioprotection (8, 17, 18).
AMP-activated Protein Kinase (AMPK)	Regulates KATP channels and mediates cardioprotection by preconditioning and 15% oxygen (8, 17).
p38 MAPK, ERK1/2, PKG	Implicated in cardioprotection (19-21).
RISK Pathway	PI3K-Akt and MEK1-ERK1/2 cascades inhibit mitochondrial permeability transition pore (22).
SAFE Pathway	Involves cytokines and STAT3, implicated in preconditioning and postconditioning (25).
HIF1α	Mediates adaptive responses to hypoxia, improves mitochondrial function and activates protective genes (27).
MicroRNAs	Modulate cardioprotective protein expression, mechanisms need further study (28).
Connexin 43 (Cx43)	Associated with ischemic preconditioning, regulates mitochondrial function (29).
Aldehyde Dehydrogenase 2	Mediator of cardioprotection, activated by PKCε and agents like isoflurane (30).
Various Proteins	Includes nitric oxide synthase, superoxide dismutase, aldose reductase, heme oxygenase (31).
Sirtuins	Promote autophagic flux, maintain mitochondrial homeostasis, and confer cardioprotection (32).

End-effectors of cardioprotection

Mitochondria serve as key end-effectors of cardioprotection, providing ATP for cellular maintenance and playing critical roles in preserving cellular integrity during stress. Regulation of mitochondrial permeability transition pore (MPTP) opening is considered a crucial cardioprotective mechanism, as well as the activation of mitochondrial ATP-sensitive K^+ (K_{ATP}) channels (33, 34).

SUR2A is a regulatory subunit of sarcolemmal K_{ATP} channels. Its expression is regulated by multiple cardioprotective signaling pathways and inhibition of an intracellular increase in SUR2A attenuates cardioprotection (35, 36).

K_{ATP} Channels Both mitochondrial and sarcolemmal ATP-sensitive potassium (K_{ATP}) channels have been implicated as end-effectors of cardioprotection. Activation of these channels modulates mitochondrial/plasma membrane potential and ion flux, contributing to cardioprotection (34-36).

Hexokinase 2, localized in mitochondria, has been shown to mediate cardioprotection by preserving mitochondrial integrity and preventing cytochrome C release during ischemia-reperfusion (37).

Nitrosation of various proteins has been observed in cardioprotection and may play a functional role in mediating protective effects (38).

The sarcoplasmic reticulum contributes to intracellular calcium homeostasis and has been implicated in cardioprotection through modulation of calcium handling and phosphorylation of regulatory proteins (39).

Cytoskeleton, cell volume, ionic balance, and pH stabilization of the cytoskeleton, regulation of cell volume, and maintenance of ionic balance and pH contribute to cardioprotection by preventing cellular injury and death (40).

Autophagy: During autophagy, organelles or metabolic wastes are swallowed into the autophagosome, which then combines with the lysosome to remove organelles or metabolic wastes to maintain cell homeostasis. Autophagy is a double-edged sword in myocardial I/R injury. The activation of autophagy during the ischemic phase removes excess metabolic waste and helps ensure cardiomyocyte survival, whereas excessive autophagy during reperfusion depletes the cellular components and leads to autophagic cell death (41).

The end-effectors of cardioprotective signaling are summarized in Table III.

Table III End-effectors of cardioprotection

Tabela III Krajnji efektori kardioprotekcije

End-effector	**Description**
Mitochondria	Key end-effectors providing ATP and preserving cellular integrity during stress. Regulation of MPTP opening and activation of mitochondrial KATP channels are crucial mechanisms (33, 34).
SUR2A	Regulatory subunit of sarcolemmal KATP channels, its expression is regulated by cardioprotective pathways. Inhibition attenuates cardioprotection (35, 36).
KATP Channels	Both mitochondrial and sarcolemmal ATP-sensitive potassium channels modulate membrane potential and ion flux, contributing to cardioprotection (34-36).
Hexokinase 2	Localized in mitochondria, mediates cardioprotection by preserving mitochondrial integrity and preventing cytochrome C release during ischemia-reperfusion (37).
Nitrosation	Nitrosation of various proteins observed in cardioprotection may play functional roles in mediating protective effects (38).
Sarcoplasmic Reticulum	Contributes to intracellular calcium homeostasis, implicated in cardioprotection through modulation of calcium handling and phosphorylation of regulatory proteins (39).
Cytoskeleton, Cell Volume, Ionic Balance, and pH	Stabilization of the cytoskeleton, regulation of cell volume, and maintenance of ionic balance and pH prevent cellular injury and death (40).
Autophagy	Maintains cell homeostasis by removing organelles or metabolic wastes. Activation during ischemia helps survival, but excessive autophagy during reperfusion can lead to cell death (41).

Future Directions

Although much has been learned about cardioprotective signaling, numerous unanswered questions remain. The spatiotemporal dynamics and interactions among signaling elements have yet to be further elucidated. A particular challenge will be to devise and develop clinically viable strategies based on cardioprotective signaling that

would serve as an adjunct to current therapeutic strategies against heart ischemia and other cardiac diseases. So far, the translation of successful animal experiments on cardioprotection into clinical settings has been largely disappointing. Animal studies are typically conducted on young, healthy animals that do not exhibit the risk factors, co-morbidities, and co-medications seen in patients with acute myocardial infarction and other conditions needing cardioprotection. There is a notable lack of experimental research on the long-term effects of cardioprotection, particularly concerning tissue repair, inflammation, remodeling, and mortality. The reproducibility and robustness of experimental studies are often affected by species differences and insufficient consideration for co-morbidities, vascular damage, inflammatory processes, and co-medications. Future research should prioritize agents/interventions with strong preclinical evidence and focus on enrolling patients who are likely to benefit from cardioprotection (see also 42).

Conclusion

In conclusion, while significant progress has been made in understanding the mechanisms of cardioprotection, many aspects of this phenomenon have yet to be fully understood. The complexity of cardioprotective signaling pathways, their interactions, and the lack of clinically tested therapeutic strategies underscore the need for continued research in this field.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

AJ wrote, reviewed, and edited the original draft.

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Kratak pregled kardioprotektivnivnih signala

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Kratak sadržaj

Kardioprotekcija se definiše kao intrinzična sposobnost srčanog tkiva da podnese izazove poput ishemijsko-reperfuzionih povreda i različitih metaboličkih stresova. Prvobitno je primećena kroz ishemijsko prekondicioniranje, ali je obim kardioprotekcije proširen tako da obuhvata i druge induktore kardioprotektivnih signala kao što su hipoksija, fluktuacije temperature i brojni farmakološki agensi, što sugeriše postojanje zajedničkih signalnih puteva i zaštitnih kaskada. Unutarćelijski faktori signalizacije koji doprinose kardioprotekciji za sada uključuju protein kinaze, putanju spašavanja reperfuzionih povreda (RISK), putanju SAFE (*Survivor Activating Factor Enhancement*), hipoksijom indukovan faktor-1α (HIF1α), mikroRNK, koneksin 43 i druge. Ovi faktori igraju uloge u aktivaciji signalnih elemenata i zaštitnih gena nizvodno, poboljšanju funkcije mitohondrija i regulisanju ekspresije proteina i citosolne funkcije kako bi omogućili kardioprotekciju. SUR2A, regulatorna podjedinica sarkolemalnih ATP-osetljivih K+ (K_{ATP}) kanala, autofagija i mitohondrije istaknuti su kao ključni krajnji efektori, sa mehanizmima poput regulacije mitohondrijalnih propusnih pora i aktivacije K_{ATP} kanala koji su ključni za kardioprotekciju. Uprkos napretku u razumevanju ovih puteva, brojni aspekti kardioprotekcije tek treba da budu bolje shvaćeni. Poseban izazov predstavlja dalje istraživanje terapijskih potencijala i, na kraju, razvoj klinički održivih strategija za zaštitu srca.

Ključne reči: kardioprotekcija, srce, ishemija, reperfuzija, kondicioniranje