Published in final edited form as:

Curr Opin Pharmacol. 2016 April ; 27: 50–55. doi:10.1016/j.coph.2016.01.006.

Mitochondrial redox status as a target for cardiovascular disease

James W. Walters^a, Deborah Amos^b, Kristeena Ray^b, and Nalini Santanam^{b,*}

^a

^b

Abstract

Mitochondria are a major player in cellular energetics, oxidative stress and programmed cell death. Mitochondrial dynamics regulates and integrates these functions. Mitochondrial dysfunction is involved in cardiac hypertrophy, hypertension and myocardial ischemia/reperfusion injury. Reactive oxygen species generation is modulated by the fusion-fission pathway as well as key proteins such as sirtuins that act as metabolic sensors of cellular energetics. Mitochondrial redox status has thus become a good target for therapy against cardiovascular diseases. Recently, there is an influx of studies garnered towards assessing the beneficial effects of mitochondrial targeted antioxidants, drugs modulating the fusion-fission proteins, sirtuins, and other mitochondrial processes as potential cardio-protecting agents.

Introduction

Mitochondria, most commonly termed the “powerhouse” of the cell got this name due to their role in energy metabolism and synthesis of adenosine tri-phosphate (ATP), the energy currency of the cell. However, in recent years it is well appreciated that mitochondria are involved in several integral physiological pathways in the cardiovascular system. This includes calcium homeostasis [1], apoptosis [2] and traumatic injury response [3,4], hence, they have gained significance in becoming a drug target for cardioprotection [5]. Mitochondria are one of the key initiators of reactive oxygen species (ROS). Electrons leak along the mitochondrial electron transport chain and oxidative phosphorylation (OXPHOS) which leads to the generation of oxygen derived free radicals, especially superoxide anion ($O_2^{\cdot-}$). During OXPHOS, energy from the nutrients are transferred to oxidized nicotinamide adenine dinucleotide (NAD^+) thus generating reduced form of nicotinamide adenine dinucleotide (NADH). When NADH is oxidized back to NAD^+ , the electrons are transferred

*Corresponding Author: Nalini Santanam, PhD, MPH, FAHA, Professor, Department of Pharmacology, Physiology & Toxicology, Department of Cardiology, Joan C Edwards School of Medicine, Marshall University, 1700 3rd Ave, 435S Byrd Biotech Research Building, Huntington, WV-25755, Tel: (304) 696-7321, Fax: (304) 696-7391, Santanam@marshall.edu (jwalters@bluefieldstate.edu) (amos23@live.marshall.edu) (ray137@live.marshall.edu)

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

back to electron acceptors and molecular oxygen to generate ATP [6]. Significant amounts of $O_2^{\cdot-}$ are produced by Complex I under two conditions, (i) when the mitochondria are not synthesizing ATP and the proton-motive force is high while the levels of coenzyme Q are low, or (ii) when the NADH/NAD⁺ ratio is high in the matrix [7]. This initial synthesis of superoxide propagates a chain reaction resulting in the synthesis of more stable and reactive free radicals such as hydrogen peroxide (H_2O_2), which in the presence of transition metals (iron-Fe or copper-Cu), can produce hydroxyl radicals ($OH^{\cdot}$) through the Fenton or Haber-Weiss reactions.

Mitochondria are also highly motile organelles and their plasticity controls their function. Evidence in the literature suggests a strong interplay between mitochondrial dynamics (fission-fusion pathways) and ROS generation [8]. Mitochondrial proteins such as the sirtuins that use NAD⁺ for their enzymatic activity also modulate the redox status [9]. In this brief review, we will outline the importance of targeting some of these pathways by drug therapies that show promising mitigation of mitochondrial dysfunction in cardiovascular disease [10]. We will highlight some of the mitochondrial targeted antioxidants, drugs modulating the fusion-fission proteins, sirtuins, as well as other mitochondrial processes.

Though mitochondria have built-in check points to prevent the generation of excess free radicals leading to oxidative stress, it is during the cascade of events following cardiac injury and atherosclerosis (i.e. ischemia/reperfusion injury (I/R)) wherein these check points are overwhelmed. Hence, there is a need to therapeutically supplement external or exogenous defense systems such as mitochondria-targeted antioxidants to increase protection or target mitochondrial dynamic pathways that exacerbate damage for cardioprotection.

Mitochondrial Antioxidants

The most well-known endogenous mitochondrial antioxidant enzyme is superoxide dismutase (SOD) which dismutates superoxide to H_2O_2 . Three forms of SOD have been identified, copper-zinc SOD, CuZnSOD (SOD1), manganese SOD, MnSOD (SOD2) and extracellular SOD, EC-SOD (SOD3). SOD2 is the form that is highly expressed in the mitochondria. SOD knockouts are embryonically lethal, however, conditional knockout studies using a Cre-lox system have identified its crucial importance in cardiomyopathy and skeletal muscle damage [11]. Though other endogenous antioxidant enzymes exist (i.e. catalase and glutathione peroxidase), the structural architecture of mitochondria prevents these and other small molecular antioxidants to enter the inner mitochondrial membrane (IMM) (see **Figure 1**). This has led to the discovery of lipophilic, cationic compounds that can penetrate the membrane potential of the mitochondrial inner and outer membrane (IMM and OMM), (some are highlighted in **Table 1**).

Mitochondrial Dynamics

Mitochondria undergo constant fusion and fission to maintain a balance between mitochondrial biogenesis and mitochondrial autophagy (mitophagy) or apoptosis [12,13]. Several of the proteins involved in mitochondrial dynamics have been well characterized. Mitofusin 1 (Mfn1), mitofusin 2 (Mfn2) and autosomal dominant optic atrophy-1 (Opa1) are

the major proteins involved in the mitochondrial fusion process. Dynamin related protein-1 (Drp1) and fission protein 1 (Fis1) are involved in the fission process. The fusion process is activated during conditions of increased mitochondrial bioenergetics. The fission process is activated during mitochondrial degradation through the autophagosome (autophagy) [14]. The nuclear protein, peroxisomal proliferative activated receptor- γ coactivator 1 α (PGC-1 α), is a key mediator of mitochondrial biogenesis and an inducer of Mfn2.

Perturbations of the IMM and OMM during ROS leakage are exacerbated by disrupted fusion and fission regulatory pathways. For instance, the dynamin related IMM protein Opa1 has been shown to maintain cristae and Opa1 +/– mice displayed enlarged mitochondria and disrupted cristae leading to cardiomyopathy [15]. Similarly, a tamoxifen-inducible cardiac-specific Drp1 knockout mouse line had mitochondrial dysfunction and impaired mitophagy leading to cardiomyopathy [16]. Interestingly, protection of cardiac tissue by lowering mitochondrial metabolism can occur with DRP1 inhibition [17]. While ablation of MFN1 in the adult heart did not cause a cardiac phenotype [18], ablation of both MFN1 and MFN2 in mice resulted in a lethal cardiomyopathy and mitochondrial fragmentation and cristae disorder [19].

Additionally, both fusion and fission proteins have been implicated in vascular smooth muscle (VSMC) proliferation and pulmonary arterial hypertension. MFN2 was found to suppress proliferation of VSMC and the concomitant increase in fatty acid oxidation and decrease in glucose oxidation [20]. Down regulation of MFN2 and PGC-1 α may lead to pulmonary arterial hypertension as MFN2 activity is needed to keep the activity of DRP1 at bay. Thus, fusion/fission proteins are potential targets for therapy. Treatment with the small molecule inhibitor of Drp1, mdivi-1, was shown to prevent the progression of pulmonary arterial hypertension [21]. It should be noted, however, that the benefits of intervention in these cases may only be short-lived as tipping the scales too far in the direction of fusion could lead to downstream complications if worn-out mitochondria cannot be cleared [13].

Thus, a deleterious feedback loop between ROS and dynamics leads to mitochondrial ROS dysfunction and subsequent apoptosis. While detrimental in any cell type, cardiomyocytes are especially vulnerable since mitochondria account for 30% of the volume of cardiomyocytes and the large myofilaments and rigid cytoskeleton likely impede their movements. This is complicated by the fact that mitochondria are damaged during I/R injury and need to be removed and replaced. Some of the drugs targeting the fusion/fission pathway are also being tested in cardiovascular diseases (see **Table 2 and Figure 1**).

Mitochondrial Sirtuins

Sirtuins are modulators of energy metabolism, DNA repair, oxidative stress and play important roles in cardiovascular disease [22]. Sirt-1 is both a nuclear and cytoplasmic protein and has been observed in mitochondria, while Sirt-3, 4, and 5 are mitochondrial proteins. Sirt-1 has been shown to regulate both biogenesis and degradation of mitochondria. Its expression decreases upon trauma and hemorrhage in rats leading to decreased PGC-1 α expression. Since PGC-1 α activates both peroxisome proliferator-activated receptor alpha (PPAR α) and nuclear respiratory factor-1 (Nrf-1) to promote mitochondrial biogenesis,

Sirt-1 modulates the creation of new mitochondria during tissue repair in cases of cardiac injury [23]. Indeed, Sirt-1 has the widest known regulatory activity among the Sirt family and can deacetylate forkhead box O (FoxO), nuclear factor- kappa B (NF- κ B), protein kinase B (Akt), and p53, thereby modulating fatty acid oxidation, cardiac hypertrophy, apoptosis, oxidative stress, and autophagy. In cardiomyocytes, activated FoxO upregulates MnSOD, catalase, and thioredoxin1, and anti-apoptotic factors, like B-cell lymphoma-extra large (Bcl-xL) [24]. Several therapeutic pharmacological activators of Sirt-1 (see **Table 2**), as well as some natural activators such as caloric restriction, stachydrine (found in citrus), omega 3 fatty acids and vitamin E are currently under clinical investigation for treatment of CVD.

NAD⁺ levels increase during starvation as well as during altered redox status, and Sirt-1 and Sirt-3 activity are part of a response to that oxidative condition. In relation to the redox status, Sirt-3 increases the transcription factor, Forkhead box O3 (FOXO3), binding to the mitochondrial superoxide scavenger genes SOD2/MnSOD, cytochrome C oxidase assembly protein (SCO2), and catalase [25], thus modulating oxidative stress. Sirt-3 can also directly activate SOD2 activity by deacetylating it [26]. To regulate ATP production, Sirt-3 also plays important roles in the electron transport chain. It interacts with and deacetylates members of Complex I. Additionally, Sirt-3 is responsible for maintaining ATP levels in the heart and kidney [27]. A component of Complex II and tricarboxylic cycle (TCA) enzyme, succinate dehydrogenase complex subunit A (SdhA), is a substrate for Sirt-3. Here, Sirt-3 stimulates succinate dehydrogenase activity lowering levels of NAD⁺ [28]. A decrease in Sirt-3 increases I/R injury, mostly in aging hearts and in pulmonary artery hypertension. Sirt-4 represses malonyl CoA decarboxylase and its knockdown results in increased β -oxidation. Due to its availability to modulate hypoxia-induced cardiomyocyte viability and apoptosis, Sirt-4 activation can be beneficial in ischemic heart disease. Sirt-5 is known to be downregulated by oxidative stress in cardiomyocytes and to act as a safeguard against ROS by reducing ROS-induced cell death [29].

Other mitochondrial targets

In addition to the targets mentioned above, there are several drugs that are being targeted to other mitochondrial proteins such as, the F1F0 ATPase inhibitors, potassium channel openers, nitric oxide analogs, drugs that target aldehyde dehydrogenase etc. (**Table 2**). Many of these compounds listed in **Table 2**, are being tested in cardiovascular diseases.

Conclusion

Mitochondria are a major player in bioenergetics but also participate in other metabolic pathways. Cardiac and vascular tissues are highly dependent on mitochondrial homeostasis. Several drugs over the years have targeted mitochondrial proteins in the hopes of providing cardioprotection. The majority of these drugs did not reach clinical significance due to limited bioavailability or toxicity. Future discovery of mitochondrial-targeted drugs will be focused on improvement in cytotoxicity and efficacy.

Acknowledgements

The authors acknowledge funding support by NIH Grant P20GM103434 (JWW and NS) to the West Virginia IDeA Network for Biomedical Research Excellence, WV-INBRE 3P20RR016477-S2 (NS) and 1R15AG051062-01 (NS). DA acknowledges funding from NASA WV-Space Grants Commission.

REFERENCES

1. Territo PR, French SA, Dunleavy MC, Evans FJ, Balaban RS. Calcium activation of heart mitochondrial oxidative phosphorylation: rapid kinetics of mVO₂, NADH, AND light scattering. *J Biol Chem*. 2001; 276:2586–2599. [PubMed: 11029457]
- 2**. Dorn GW 2nd, Kitsis RN. The mitochondrial dynamism-mitophagy-cell death interactome: multiple roles performed by members of a mitochondrial molecular ensemble. *Circ Res*. 2015; 116:167–182. [PubMed: 25323859] [This review highlights the interplay between the various mitochondrial functions and its relevance to cardiomyocyte and cardiac development.]
3. Ong SB, Hausenloy DJ. Mitochondrial morphology and cardiovascular disease. *Cardiovasc Res*. 2010; 88:16–29. [PubMed: 20631158]
4. Disatnik MH, Ferreira JC, Campos JC, Gomes KS, Dourado PM, Qi X, Mochly-Rosen D. Acute inhibition of excessive mitochondrial fission after myocardial infarction prevents long-term cardiac dysfunction. *J Am Heart Assoc*. 2013; 2:e000461. [PubMed: 24103571]
5. Dongworth RK, Hall AR, Burke N, Hausenloy DJ. Targeting mitochondria for cardioprotection: examining the benefit for patients. *Future Cardiol*. 2014; 10:255–272. [PubMed: 24762253]
- 6*. Dodson M, Darley-Usmar V, Zhang J. Cellular metabolic and autophagic pathways: traffic control by redox signaling. *Free Radic Biol Med*. 2013; 63:207–221. [PubMed: 23702245] [This article highlights the relationship between metabolic pathways, oxidative phosphorylation and the generation of reactive oxygen species.]
7. Adam-Vizi V, Tretter L. The role of mitochondrial dehydrogenases in the generation of oxidative stress. *Neurochem Int*. 2013; 62:757–763. [PubMed: 23357482]
8. Wohlgemuth SE, Calvani R, Marzetti E. The interplay between autophagy and mitochondrial dysfunction in oxidative stress-induced cardiac aging and pathology. *J Mol Cell Cardiol*. 2014; 71:62–70. [PubMed: 24650874]
- 9*. Cencioni C, Spallotta F, Mai A, Martelli F, Farsetti A, Zeiher AM, Gaetano C. Sirtuin function in aging heart and vessels. *J Mol Cell Cardiol*. 2015; 83:55–61. [PubMed: 25579854] [Sirtuins are key metabolic regulators. This article focuses on the role of sirtuins in cardioprotection.]
- 10**. Schwarz K, Siddiqi N, Singh S, Neil CJ, Dawson DK, Frenneaux MP. The breathing heart - mitochondrial respiratory chain dysfunction in cardiac disease. *Int J Cardiol*. 2014; 171:134–143. [PubMed: 24377708] [This article explains how mitochondrial dysfunction leads to cardiac disorders and reviews pharmacological and non-pharmacological strategies to thwart it.]
11. Koyama H, Nojiri H, Kawakami S, Sunagawa T, Shirasawa T, Shimizu T. Antioxidants improve the phenotypes of dilated cardiomyopathy and muscle fatigue in mitochondrial superoxide dismutase-deficient mice. *Molecules*. 2013; 18:1383–1393. [PubMed: 23348992]
- 12*. Archer SL. Mitochondrial dynamics--mitochondrial fission and fusion in human diseases. *N Engl J Med*. 2013; 369:2236–2251. [PubMed: 24304053] [This is a very well written review that describes the process of mitochondrial dynamics (fission-fusion pathways) and how its dysfunction can contribute to the pathogenesis of complex diseases.]
13. Ong SB, Kalkhoran SB, Cabrera-Fuentes HA, Hausenloy DJ. Mitochondrial fusion and fission proteins as novel therapeutic targets for treating cardiovascular disease. *Eur J Pharmacol*. 2015; 763:104–114. [PubMed: 25987420]
14. Westermann B. Bioenergetic role of mitochondrial fusion and fission. *Biochim Biophys Acta*. 2012; 1817:1833–1838. [PubMed: 22409868]
15. Chen L, Liu T, Tran A, Lu X, Tomilov AA, Davies V, Cortopassi G, Chiamvimonvat N, Bers DM, Votruba M, et al. OPA1 mutation and late-onset cardiomyopathy: mitochondrial dysfunction and mtDNA instability. *J Am Heart Assoc*. 2012; 1:e003012. [PubMed: 23316298]

16. Ikeda Y, Shirakabe A, Maejima Y, Zhai P, Sciarretta S, Toli J, Nomura M, Mihara K, Egashira K, Ohishi M, et al. Endogenous Drp1 mediates mitochondrial autophagy and protects the heart against energy stress. *Circ Res.* 2015; 116:264–278. [PubMed: 25332205]
17. Zepeda R, Kuzmicic J, Parra V, Troncoso R, Pennanen C, Riquelme JA, Pedrozo Z, Chiong M, Sanchez G, Lavandero S. Drp1 loss-of-function reduces cardiomyocyte oxygen dependence protecting the heart from ischemia-reperfusion injury. *J Cardiovasc Pharmacol.* 2014; 63:477–487. [PubMed: 24477044]
18. Papanicolaou KN, Ngoh GA, Dabkowski ER, O'Connell KA, Ribeiro RF Jr, Stanley WC, Walsh K. Cardiomyocyte deletion of mitofusin-1 leads to mitochondrial fragmentation and improves tolerance to ROS-induced mitochondrial dysfunction and cell death. *Am J Physiol Heart Circ Physiol.* 2012; 302:H167–179. [PubMed: 22037195]
19. Papanicolaou KN, Kikuchi R, Ngoh GA, Coughlan KA, Dominguez I, Stanley WC, Walsh K. Mitofusins 1 and 2 are essential for postnatal metabolic remodeling in heart. *Circ Res.* 2012; 111:1012–1026. [PubMed: 22904094]
20. Zhou W, Chen KH, Cao W, Zeng J, Liao H, Zhao L, Guo X. Mutation of the protein kinase A phosphorylation site influences the anti-proliferative activity of mitofusin 2. *Atherosclerosis.* 2010; 211:216–223. [PubMed: 20303493]
21. Marsboom G, Toth PT, Ryan JJ, Hong Z, Wu X, Fang YH, Thenappan T, Piao L, Zhang HJ, Pogoriler J, et al. Dynamin-related protein 1-mediated mitochondrial mitotic fission permits hyperproliferation of vascular smooth muscle cells and offers a novel therapeutic target in pulmonary hypertension. *Circ Res.* 2012; 110:1484–1497. [PubMed: 22511751]
22. Matsushima S, Sadoshima J. The role of sirtuins in cardiac disease. *Am J Physiol Heart Circ Physiol.* 2015;ajpheart 00053 02015.
23. Zhang Y, Mi SL, Hu N, Doser TA, Sun A, Ge J, Ren J. Mitochondrial aldehyde dehydrogenase 2 accentuates aging-induced cardiac remodeling and contractile dysfunction: role of AMPK, Sirt1, and mitochondrial function. *Free Radic Biol Med.* 2014; 71:208–220. [PubMed: 24675227]
24. Hsu CP, Zhai P, Yamamoto T, Maejima Y, Matsushima S, Hariharan N, Shao D, Takagi H, Oka S, Sadoshima J. Silent information regulator 1 protects the heart from ischemia/reperfusion. *Circulation.* 2010; 122:2170–2182. [PubMed: 21060073]
25. Verdin E, Hirschey MD, Finley LW, Haigis MC. Sirtuin regulation of mitochondria: energy production, apoptosis, and signaling. *Trends Biochem Sci.* 2010; 35:669–675. [PubMed: 20863707]
26. Qiu X, Brown K, Hirschey MD, Verdin E, Chen D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. *Cell Metab.* 2010; 12:662–667. [PubMed: 21109198]
27. Finkel T, Menazza S, Holmstrom KM, Parks RJ, Liu J, Sun J, Liu J, Pan X, Murphy E. The ins and outs of mitochondrial calcium. *Circ Res.* 2015; 116:1810–1819. [PubMed: 25999421]
28. Cimen H, Han MJ, Yang Y, Tong Q, Koc H, Koc EC. Regulation of succinate dehydrogenase activity by SIRT3 in mammalian mitochondria. *Biochemistry.* 2010; 49:304–311. [PubMed: 20000467]
29. Liu B, Che W, Zheng C, Liu W, Wen J, Fu H, Tang K, Zhang J, Xu Y. SIRT5: a safeguard against oxidative stress-induced apoptosis in cardiomyocytes. *Cell Physiol Biochem.* 2013; 32:1050–1059. [PubMed: 24192575]
30. Yancey DM, Guichard JL, Ahmed MI, Zhou L, Murphy MP, Johnson MS, Benavides GA, Collawn J, Darley-USmar V, Dell'Italia LJ. Cardiomyocyte mitochondrial oxidative stress and cytoskeletal breakdown in the heart with a primary volume overload. *Am J Physiol Heart Circ Physiol.* 2015; 308:H651–663. [PubMed: 25599572]
- 31*. Lukashev AN, Skulachev MV, Ostapenko V, Savchenko AY, Pavshintsev VV, Skulachev VP. Advances in development of rechargeable mitochondrial antioxidants. *Prog Mol Biol Transl Sci.* 2014; 127:251–265. [PubMed: 25149221] [Mitochondrial targeted antioxidants have been tested and tried in several formats. Though successful in animal models, these compounds have limitations in humans. This article summarizes the advances being made in developing better mitochondrial antioxidants for human use.]
32. Szeto HH. Mitochondria-targeted cytoprotective peptides for ischemia-reperfusion injury. *Antioxid Redox Signal.* 2008; 10:601–619. [PubMed: 17999629]

33. Liu Y, Wu H, Chong Y, Wamer WG, Xia Q, Cai L, Nie Z, Fu PP, Yin JJ. Platinum Nanoparticles: Efficient and Stable Catechol Oxidase Mimetics. *ACS Appl Mater Interfaces*. 2015; 7:19709–19717. [PubMed: 26305170]
34. Yue W, Chen Z, Liu H, Yan C, Chen M, Feng D, Yan C, Wu H, Du L, Wang Y, et al. A small natural molecule promotes mitochondrial fusion through inhibition of the deubiquitinase USP30. *Cell Res*. 2014; 24:482–496. [PubMed: 24513856]
35. Mellini P, Valente S, Mai A. Sirtuin modulators: an updated patent review (2012 - 2014). *Expert Opin Ther Pat*. 2015; 25:5–15. [PubMed: 25435179]
36. Yang M, Stowe DF, Udoh KB, Heisner JS, Camara AK. Reversible blockade of complex I or inhibition of PKC β reduces activation and mitochondria translocation of p66Shc to preserve cardiac function after ischemia. *PLoS One*. 2014; 9:e113534. [PubMed: 25436907]
37. Lindsay DP, Camara AK, Stowe DF, Lubbe R, Aldakkak M. Differential effects of buffer pH on Ca(2+)-induced ROS emission with inhibited mitochondrial complexes I and III. *Front Physiol*. 2015; 6:58. [PubMed: 25805998]
38. Shen Y, Shen Z, Luo S, Guo W, Zhu YZ. The Cardioprotective Effects of Hydrogen Sulfide in Heart Diseases: From Molecular Mechanisms to Therapeutic Potential. *Oxid Med Cell Longev*. 2015; 2015:925167. [PubMed: 26078822]
39. Kuno A, Tanno M, Horio Y. The effects of resveratrol and SIRT1 activation on dystrophic cardiomyopathy. *Ann N Y Acad Sci*. 2015; 1348:46–54. [PubMed: 26109180]
40. Yao Z, Hu W, Yin S, Huang Z, Zhu Q, Chen J, Zang Y, Dong L, Zhang J. 3,3'-Diindolymethane ameliorates adriamycin-induced cardiac fibrosis via activation of a BRCA1-dependent anti-oxidant pathway. *Pharmacol Res*. 2013; 70:139–146. [PubMed: 23376355]
41. Paradis S, Leoni V, Caccia C, Berdeaux A, Morin D. Cardioprotection by the TSPO ligand 4'-chlorodiazepam is associated with inhibition of mitochondrial accumulation of cholesterol at reperfusion. *Cardiovasc Res*. 2013; 98:420–427. [PubMed: 23554458]
42. Bernardi P, Di Lisa F. The mitochondrial permeability transition pore: molecular nature and role as a target in cardioprotection. *J Mol Cell Cardiol*. 2015; 78:100–106. [PubMed: 25268651]
43. Schaller S, Paradis S, Ngoh GA, Assaly R, Buisson B, Drouot C, Ostuni MA, Lacapere JJ, Bassissi F, Bordet T, et al. TRO40303, a new cardioprotective compound, inhibits mitochondrial permeability transition. *J Pharmacol Exp Ther*. 2010; 333:696–706. [PubMed: 20215409]
44. Nadtochiy SM, Zhu Q, Urciuoli W, Rafikov R, Black SM, Brookes PS. Nitroalkenes confer acute cardioprotection via adenine nucleotide translocase 1. *J Biol Chem*. 2012; 287:3573–3580. [PubMed: 22158628]
45. Petrus A, Duicu OM, Sturza A, Noveanu L, Kiss L, Danila M, Baczko I, Muntean DM, Jost N. Modulation of mitochondrial respiratory function and ROS production by novel benzopyran analogues. *Can J Physiol Pharmacol*. 2015; 93:811–818. [PubMed: 26325241]
46. Silachev DN, Gulyaev MV, Zorova LD, Khailova LS, Gubsky LV, Pirogov YA, Plotnikov EY, Sukhikh GT, Zorov DB. Magnetic resonance spectroscopy of the ischemic brain under lithium treatment. Link to mitochondrial disorders under stroke. *Chem Biol Interact*. 2015; 237:175–182. [PubMed: 26079057]
47. Henninger C, Huelsenbeck S, Wenzel P, Brand M, Huelsenbeck J, Schad A, Fritz G. Chronic heart damage following doxorubicin treatment is alleviated by lovastatin. *Pharmacol Res*. 2015; 91:47–56. [PubMed: 25462173]
48. He L, Liu B, Dai Z, Zhang HF, Zhang YS, Luo XJ, Ma QL, Peng J. Alpha lipoic acid protects heart against myocardial ischemia-reperfusion injury through a mechanism involving aldehyde dehydrogenase 2 activation. *Eur J Pharmacol*. 2012; 678:32–38. [PubMed: 22266491]
49. Gomes KM, Campos JC, Bechara LR, Queliconi B, Lima VM, Disatnik MH, Magno P, Chen CH, Brum PC, Kowaltowski AJ, et al. Aldehyde dehydrogenase 2 activation in heart failure restores mitochondrial function and improves ventricular function and remodelling. *Cardiovasc Res*. 2014; 103:498–508. [PubMed: 24817685]
50. Palaniswamy C, Mellana WM, Selvaraj DR, Mohan D. Metabolic modulation: a new therapeutic target in treatment of heart failure. *Am J Ther*. 2011; 18:e197–201. [PubMed: 20393344]

Highlights

- Mitochondrial ROS and dynamics play a role in cardiovascular diseases
- Mitochondrial fusion-fission pathways regulate cardiomyocyte function
- Mitochondrial targets are useful in cardioprotection

Figure 1. Mitochondrial dynamics within a cardiomyocyte

A. Diagram of cardiomyocyte mitochondrial architecture within the myofibrils. a. capillary and red blood cell, b. lysosome, c. closely packed mitochondria between myofibril layers, d. Z disks, A band, I band, and M Line of myofibrils, e. mitochondria undergoing autophagy (mitophagy). **B.** Fusion and fission targets and their respective therapeutic drugs. **C.** Diagram of reactive oxygen production and scavenging in relation to mitochondrial fusion and fission proteins (DRP1, Fis1, Mfn1, Mfn2 OPA1) and Sirt regulators of apoptosis, ROS regulation and fusion and fission.

TABLE 1

Mitochondrial targeted antioxidants:

Class	Compounds	Mechanism of action and Relevance to CVD	Ref
Triphenylphosphonium (TPP) Derivatives:	<i>MitoQ</i>	It consists of a TPP attached to the ubiquinone moiety of the CoQ10. Scavenges superoxide, peroxyl and peroxynitrite. I/R, spontaneous hypertension, fatty liver and other kidney diseases	[30]
	MitoTempol, MitoVitE, MitoPBN	Either directly act as SOD mimetic (MitoTempol) by scavenging O ²⁻ or by detoxifying Fenton reactions, others (Mito VitE and MitoPBN) act more on preventing lipid peroxidation either as a chain-breaking antioxidant or scavenging carbon-centered radicals. I/R, hypertension	[30]
Skulachev-ion derivatives	SkQ1	TPP conjugated to plastoquinone acts by either recycling the fatty acids thus creating a mild uncoupling reaction or by preventing lipid oxidation of cardiolipin. I/R	[31]
Szeto-Schiller peptides	SS-01, SS-20, SS-31	Small aromatic-cationic peptides scavenge H ₂ O ₂ , peroxynitrite and inhibit lipid peroxidation (probably attributed to the tyrosine residues). MI, hypertension	[32]
SOD/catalase mimetics	Salen Mn complexes, EUK-134, EUK-189, EUK-207	I/R, hypertension	[33]

Table 2
Mitochondrial targeted drugs in consideration for cardiovascular diseases (CVD)

Number	Mito Target	Drug Name	Relevance in CVD	References
1	Mitochondrial fission/fusion drugs	DRP1, Opa1 targets- mdivi-1, Dynasore, P110, Mfn targets- S3 (15-oxospiramylactone)	I/R injury, inhibits proliferation	[13,21]
2	Sirtuins	SRT2104 and SRT2379, SRT1720, SRT2379	Metabolic diseases, atherosclerosis	[34]
3	Respiratory chain inhibitors	Complex I- Amobarbital, Metformin, Rotenone	I/R, TIA, ischemic stroke	[35]
		Complex III- Antimycin A, Myxothiazole	I/R	[36]
		Complex IV-H₂S (Complex IV)	MI, arrhythmia, hypertrophy, fibrosis, IR and Heart failure	[37]
4	F1F0-ATPase inhibitors/Proton channel blockers	Aurovertin, Resveratrol	Ischemia, I/R, cardiomyopathy	[38]
		PK1119, Bz-423, Diindolyl methane, Apoptolidin, Oligomycin	Cardiac fibrosis	[39]
		4'-chlorodiazepam (ro5-4684)	Arrhythmia, I/R	[40]
5	PT pore inhibitors	Cyclosporin (CsA), Sanglifehrin A, Debio 025, NIM811	Reperfusion injury, Post-MI injury	[41]
		TRO40303	I/R	[42]
6	NO analogs	MitoSNO1, Nitrolipids, Nitrite, SNO-MPG	I/R, CHF	[43]
7	Potassium channel openers	Atenolol A5, BMS-191095, Cromakalim, Diazoxide, Malonate, Minoxidil, NS11021, NS1619, Pinacidil	I/R, MI, infarct size-limiting effect of ischemic preconditioning, myocardial reperfusion hyperoxygenation, improved cardiac contractile activity	[44]
8	RISK pathway modulators	Lithium, SB216763	Ischemic stroke, I/R	[45]
		Statins	prevent acute life-threatening coronary events	[46]
9	Aldehyde dehydrogenase 2	alpha-lipoic acid	Hypertension, I/R,	[47]
		Alda1	ventricular functioning/HF	[48]
10	Metabolic modulators	A-769662, Acadesine (AICAR), DCA, Etomoxir, GIK, Idebenone, L-arginine, Oxfenicine, perhexiline, ranolazine, trimetazidine	Hypertension, Ischemia, heart remodeling,	[49]
				[50]