



Invited Review Article

Regulation of Nrf2 signaling pathway in heart failure: Role of extracellular vesicles and non-coding RNAs[☆]Changhai Tian^a, Lie Gao^b, Irving H. Zucker^{b,*}^a Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5880, USA^b Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE, 68198-5850, USA

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ABSTRACT

The balance between pro- and antioxidant molecules has been established as an important driving force in the pathogenesis of cardiovascular disease. Chronic heart failure is associated with oxidative stress in the myocardium and globally. Redox balance in the heart and brain is controlled, in part, by antioxidant proteins regulated by the transcription factor Nuclear factor erythroid 2-related factor 2 (Nrf2), which is reduced in the heart failure state. Nrf2 can, in turn, be regulated by a variety of mechanisms including circulating microRNAs (miRNAs) encapsulated in extracellular vesicles (EVs) derived from multiple cell types in the heart. Here, we review the role of the Nrf2 and antioxidant enzyme signaling pathway in mediating redox balance in the myocardium and the brain in the heart failure state. This review focuses on Nrf2 and antioxidant protein regulation in the heart and brain by miRNA-enriched EVs in the setting of heart failure. We discuss EV-mediated intra- and inter-organ communications especially, communication between the heart and brain via an EV pathway that mediates cardiac function and sympatho-excitation in heart failure. Importantly, we speculate how engineered EVs with specific miRNAs or antagomirs may be used in a therapeutic manner in heart failure.

1. Introduction

While this review will focus on the role of extracellular vesicles (EVs) in the regulation of Nuclear factor erythroid 2-related factor 2 (Nrf2), antioxidant enzymes and oxidative stress in heart failure, it is necessary to also discuss the role of non-coding RNA in the regulation of Nrf2 in tissues outside of the heart. We will therefore, provide an overview of these mechanisms prior to a discussion of the role played by EVs, including exosomes and microvesicles in inter and intra organ communication.

Chronic heart failure (CHF) is a major cause of mortality and morbidity worldwide, and is a growing public health concern due, in part, to aging and obesity in the contemporary population [1,2] and the growing incidence of Type 2 diabetes [3]. Based on data from NHANES (National Health and Nutrition Examination Survey; 2011 to 2014), an estimated 6.5 million Americans ≥ 20 years of age suffer from CHF. Projections show that the prevalence of CHF will increase by 46% by 2030, resulting in >8 million people ≥ 18 years of age suffering from some form of CHF. These data also predict that the total cost of CHF will increase almost 127%, to \$69.7 billion from 2012, amounting to \approx \$244

Abbreviations: Angiotensin II, (Ang II); Angiotensinogen, (Agt); Antioxidant response element, (ARE); Antioxidant enzymes, (AO); ARE-like sequence 1/2, (AREL1/2); Autophagy-related genes, (Atgs); Brahma-related gene 1, (BRG1); Central nervous system, (CNS); Chronic heart failure, (CHF); CREB-binding protein, (CBP); Cullin 3, (CUL3); Cysteine-rich protein 2, (CRIP2); α -crystallin B, (CRYAB); DNA methyltransferases, (DNMTs); Endoplasmic reticulum, (ER); Extracellular vesicles, (EVs); Fructosamine-3-kinase, (FN3K); Glycogen synthase kinase-3, (GSK-3 β); Heme oxygenase 1, (HO-1); Histone acetyltransferases, (HATs); Histone deacetylases, (HDACs); Hypoxia/Reoxygenation, (H/R); Ischemia/reperfusion, (I/R); Kelch Like ECH Associated Protein 1, (Keap1); Long non-coding RNAs, (lncRNAs); Lysine Acetyltransferase 8, (KAT8); Myocardial infarction, (MI); NADPH Oxidase, (Nox2); NADPH Oxidase Quinone 1, (NQO-1); Non-coding RNAs, (ncRNAs); NOD- LRR- and pyrin domain-containing protei, (NLRP); Nuclear factor erythroid 2-related factor 2, Nrf2); Reactive oxygen species, (ROS); Renin angiotensin aldosterone system, (RAAS); RNA polymerase II, (RNAP II); Rostral ventrolateral medulla, (RVLM); Sirtuin 6, (SIRT6); Sympathetic nerve activity, (SNA); Transverse aortic constriction, (TAC); Ubiquitination, (Ub).

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for every adult in the United States [4,5].

Therapy for CHF has changed only modestly over the last 30 years. While surgical and device therapies have grown, there have not been any major changes in medical treatment since drugs were developed and used to block the renin-angiotensin-aldosterone system (RAAS) and the autonomic nervous system (e.g. beta-1 adrenergic blockers); both of which have clearly improved long-term survival [6]. However, 5-year survival for CHF is still only approximately 50%. These are sobering statistics that behooves the medical and scientific community to understand the complexity of this syndrome in all organ systems in order to identify new and effective therapies.

The mechanisms by which cardiovascular (CV) function spirals downward in the heart failure state are multifactorial, involving almost every organ system. It has been well established that oxidative stress is a major contributor to the pathogenesis of heart failure [7–9]. An imbalance between the synthesis of oxygen free radicals and their elimination by antioxidant defense mechanisms results in macromolecular damage and disruption of cellular redox signaling [10,11], thus affecting both cardiac structure and function [12–14] as well as remote targets. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a highly conserved transcription factor regulating antioxidant enzymes, phase II detoxifying enzymes and other detoxification proteins by direct binding to the antioxidant response elements (AREs) in their promoter regions [15,16]. The critical roles of the Nrf2/ARE signaling pathway in various physiological and pathophysiological conditions through both anti-inflammatory and anti-oxidant mechanisms has been well-documented [17]. In addition, many Nrf2-regulated enzymes have been implicated in the pathogenesis of CV diseases and are strongly associated with oxidative stress-mediated cardiac remodeling and heart failure [18–20]. Nrf2-regulated enzymes may also serve as sensitive and specific markers reflecting ventricular function in heart failure patients [21].

Recently, systemic Nrf2 activation has been shown to be beneficial in CV disease [22,23], while Nrf2 knock-out mice have no effects on growth or development and on cardiac structure and function under normal conditions [24,25]. Global deficiency of Nrf2 in mice facilitates transverse aortic constriction (TAC)-induced cardiac dysfunction, including cardiac hypertrophy, fibrosis and apoptosis, overt heart failure, and increased mortality [24]. These mice are susceptible to angiotensin II-induced cardiac hypertrophy [26]. Many of these events can be attributed to elevated myocardial oxidative stress. Cardiac-specific overexpression of Nrf2 in mice is cardio-protective resulting in the smaller infarct size, less cardiac fibrosis and inflammation induced, in part, by stabilizing the Keap1-Nrf2 complex and enhancing Nrf2 nuclear translocation and subsequent inhibition of pro-oxidant pathways [27]. Because sympatho-excitation is a hallmark of the heart failure state the role of oxidative stress and Nrf2 in the brainstem is of high relevance. Selective deletion of Nrf2 in areas of the brain that modulate sympathetic outflow results in sustained hypertension in normal mice [28]. Selective activation or overexpression of Nrf2 in the brain reduces sympatho-excitation in the setting of heart failure [29,30]. Overall, these studies suggest that the Nrf2/ARE signaling pathway plays a critical role in maintaining redox homeostasis in the heart and brain in the heart failure state. Thus, it is important to understand the regulation of Nrf2 in heart failure in order to develop novel therapeutic strategies in the treatment of this disease.

Increasing evidence suggest that the regulation of the Nrf2/ARE signaling pathway in the progression of heart failure is multi-faced, involving protein-protein interactions and epigenetic regulation. Interestingly, EVs, generally classified into exosomes, microvesicles or apoptotic bodies, are found to serve as carriers of biological messages in various pathophysiological settings, including heart failure [31–33]. The focus of this review will also be on the role of cardiac-derived EVs and their cargo (microRNAs, proteins, small molecules) in the CHF state with particular emphasis on the regulation of Nrf2 and oxidant stress in the heart and remote tissues.

2. Regulation of Nrf2/Antioxidant response element (ARE) signaling by protein-protein interactions

The Kelch-like-ECH-associated protein 1 (Keap1)-Nrf2 system is a thiol-based sensor-effector apparatus for maintaining redox homeostasis. Keap1-Nrf2 forms a major node of cellular and organismal defense against oxidative and electrophilic stresses of both exogenous and endogenous origins and plays an important role in the progression of disease [34]. Under normal conditions (i.e. low levels of oxidant stress), Nrf2 is bound in the cytoplasm by Keap1 and Cullin 3, working together to regulate the ubiquitination of Nrf2 [35]. Oxidative stress can directly target critical cysteine residues in Keap1, resulting in degradation of the Keap1-Cullin 3 ubiquitination system. In addition, p62 physically interacts with Keap1 [36,37] through its STGE motif, similar with that of Nrf2 to mediate autophagic degradation of Keap1, resulting in the dissociation of Nrf2 from Keap1 and formation of unbound/free Nrf2 [38]. Oxidative stress-mediated activation of Nrf2 has been attributed to the phosphorylation of the p62 STGE motif at Ser349 by mTORC1 enhancing the binding of p62 to Keap1 and subsequent Keap1 autophagic degradation indirectly increasing Nrf2 [39–42]. Once Nrf2 is released from Keap1, it translocates to the nucleus where it either binds to AREs in the promoters of target genes thereby activating their expression [43,44] or directly binds its own ARE-like elements located in the proximal region of its promoter to auto-regulate its own transcription and subsequently enhance the expression of downstream target genes [16]. Thus, Nrf2 can be considered an “amplifier” of anti-oxidant pathways.

In addition to Keap1-dependent ubiquitination and proteasomal degradation of Nrf2, an increasing body of literature has demonstrated alternative mechanisms of Nrf2 regulation, including the phosphorylation of Nrf2 by various protein kinases [45–49], direct acetylation of Nrf2 by histone acetyltransferases (HATs) [50] and de-glycation by Fructosamine-3-Kinase (FN3K) [51]. These mechanisms enhance the nuclear retention and ARE binding of Nrf2 [52–54], and its interaction with other protein partners [51,55–61]. These are potentially important determinants of Nrf2 activity and function, and therefore contribute to the maintenance of cellular redox homeostasis in heart failure (as illustrated in Fig. 1).

It has been reported that the small heat-shock protein α -crystallin B (CRYAB) acts as a molecular switch in determining endoplasmic reticulum (ER) stress-induced cardiomyocyte apoptosis following myocardial infarction (MI) [58]. A mechanistic study from the same laboratory showed that as a direct target of p38 MAPK, the deactivation of CRYAB changed in parallel with Nrf2 and was observed in p38 MAPK inhibitor-treated MI rats [62], suggesting p38 MAPK-mediated cardio-protective effects may rely on the interplay between Nrf2 and CRYAB. Interestingly, the pathogenesis of heart failure has also been associated with some inheritable mutations in CRYAB, such as R120GCRYAB causing protein aggregation cardiomyopathy (PAC) [63]. Further mechanistic study revealed that this mutation causes increased ROS and protein aggregation contributing to the dissociation of Keap1 from Nrf2 and constitutive activation of Nrf2, promoting “reductive stress (RS)” due to the dysregulation of glutathione homeostasis. Increasing evidence suggests RS can cause endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) [64]. UPR signaling can not only trigger ROS generation from the ER and the mitochondria, which will sulfenylate a cysteine of IRE-1 (Inositol-requiring enzyme 1, ER stress sensor) [65], but can also activate Nrf2 signaling by phosphorylation mediated by the IRE1-TRAF2-ASK1-JNK pathway [66]. These novel findings suggest that chronic RS caused by constitutive Nrf2 activation may contribute to the pathogenesis of heart failure, and is indicative of the “dark side” of Nrf2 which must be taken account when we develop antioxidant-based therapeutic strategies.

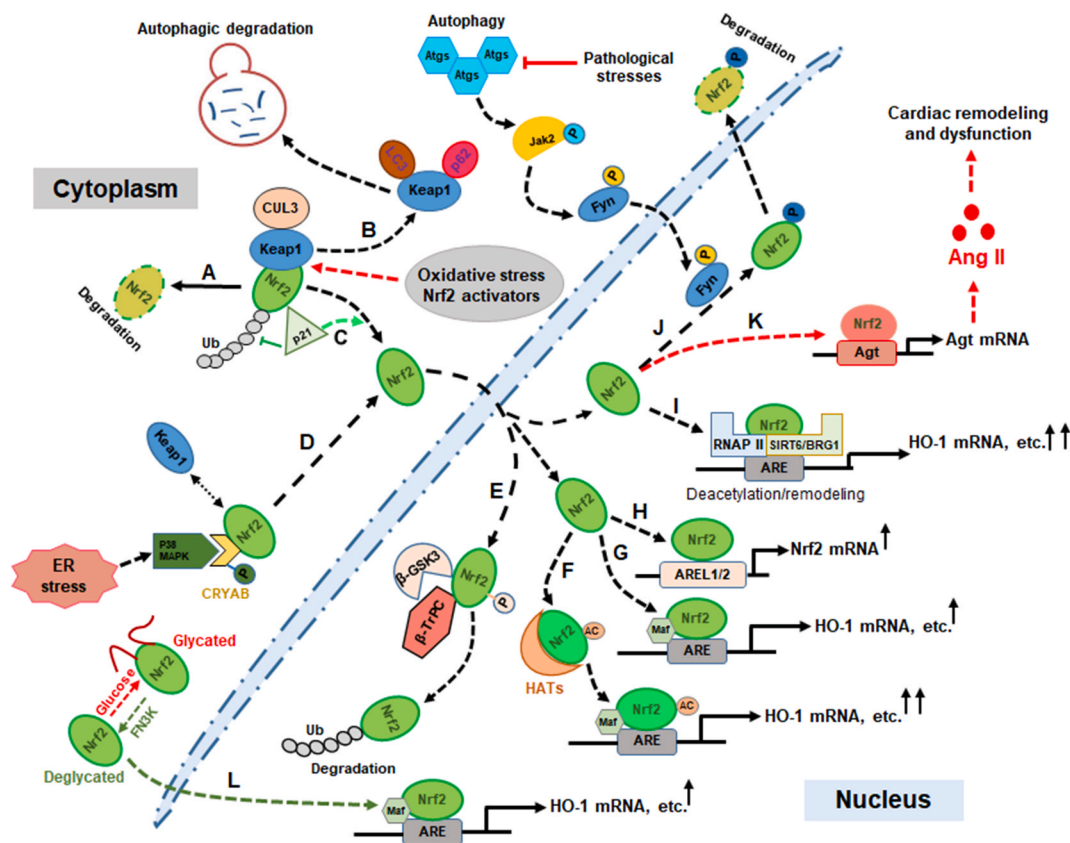


Fig. 1. Schematic diagram of potential mechanisms by which Nrf2 signaling is regulated via protein interplay as a therapeutic process and in the pathogenesis of heart failure. Keap1-dependent Nrf2 degradation in the normal condition (A); Autophagic degradation of Keap1 (B); p21 (Cip1/WAF1)-mediated inhibition of Nrf2 ubiquitination (C); ER stress-mediated Nrf2 activation by the p38 MAPK-CRYAB axis (D); β -GSK3 β - β -TrPC-mediated Nrf2 ubiquitination and nuclear degradation (E); HAT-mediated Nrf2 acetylation and enhanced transcriptional activation of downstream targets (F); the Nrf2 canonical activation pathway (G); Nrf2 acts as an “Amplifier” via self-activation (H); Transcriptional enhancements of Nrf2 targets by Nrf2-SIRT6/BRG1-RNAPII complex-mediated ARE deacetylation or chromatin remodeling (I); Fine regulation of Nrf2 nuclear accumulation by autophagic signaling (J); Autophagic impairment initiates Nrf2 detrimental effects by activating angiotensinogen expression and subsequent pathophysiological alterations (K); The de-glycation of Nrf2 protein by FN3K enhances its stability and binding to small MAF protein and subsequent transcriptional activation (L). Abbreviations: Histone NAD(+)-dependent deacetylase 6 (SIRT6); Heme oxygenase 1 (HO-1); α -crystallin B (CRYAB); Glycogen synthase kinase-3 (GSK-3 β); RNA polymerase II (RNAP II); Brahma-related gene 1 (BRG1); Endoplasmic reticulum (ER); Histone acetyltransferases (HATs); Antioxidant response element (ARE); Autophagy-related genes (Atg); Ubiquitination (Ub); Angiotensinogen (Agt); Angiotensin II (Ang II); Autophagy-related genes (Atgs); ARE-like sequence 1/2 (AREL1/2); Cullin 3 (CUL3); Fructosamine-3-kinase (FN3K).

3. Epigenetic regulation of Nrf2/ARE signaling pathway in heart failure

In addition to genetic regulation, epigenetic regulation plays an important role in gene expression. This includes DNA methylation, histone methylation and acetylation, non-coding RNAs, and chromatin remodeling [67,68]. Relevant to this review, epigenetic mechanisms have been involved in oxidative stress during mutagenesis [69–71]. Numerous Nrf2 chemical activators have also been identified to activate downstream gene expression by epigenetic mechanisms [72,73]. Mounting evidence suggests that epigenetic regulation plays a critical role in the pathogenesis of heart failure [74–77]. As a master regulator of redox homeostasis, the idea that Nrf2/ARE signaling is genetically regulated in the pathophysiological progression of heart failure is attracting much attention, increasing evidence suggests that this epigenetic regulation of the Nrf2/ARE signaling pathway are also involved in heart failure [23,60,78–81] (see Table 1).

3.1. DNA methylation of Nrf2/ARE signaling in heart failure

Recent studies in diabetic animals have identified cardiomyocyte dysfunction as an important mediator of heart failure, which was attributed to the demethylation of CpG islands within the Keap1

promoter, and subsequent overexpression of Keap1 and proteosomal degradation of Nrf2 as well as alterations of redox hemostasis [78]. Conversely, the demethylation of CpG islands in the promoter of Nrf2 is required for Nrf2 transcriptional activation. Tanshinone IIA (TIIA), a bioactive compound isolated from *Salvia miltiorrhiza*, has been reported to have a cyto-protective function against oxidative stress, myocardial ischemic injury and inflammation [82–86]. Molecular studies suggest that the cyto-protective effects of TIIA can be attributed to Nrf2 signaling activation and its downstream target gene expression [79,82]. Further evidence indicates that TIIA induces the degradation of Keap1 protein without effects on Keap1 transcription and directly inhibits the activity of DNA methyltransferases (DNMTs) resulting in the upregulation of Nrf2 and downstream genes in ventricular myocytes and subsequent inhibition of myocardial apoptosis [79]. These studies suggest that methylation/demethylation regulation of the Keap1/Nrf2 signaling axis may be potential targets for heart failure therapy.

3.2. Histone modifications of Nrf2/ARE signaling in heart failure

Alterations in histone modifications also impact DNA accessibility to transcriptional machinery and other regulatory factors in human diseases [87,88]. It has been well-documented that histone acetyltransferases (HATs) and deacetylases (HDACs) can control Nrf2 activity

Table 1

Epigenetic regulation of Nrf2/ARE signaling pathway in heart failure.

Target	Epigenetic type	Experimental Model	Mechanisms and outcomes	References
Keap1 promoter	Demethylation of CpG island	Diabetic cardiomyopathy patients	Failure of Nrf2 mediated antioxidant system	[78]
Nrf2 promoter	Demethylation of CpG island	Cardiomyocytes; TAC mouse model	Nrf2 transcriptional activation	[79,83,85]
Nrf2 protein	Potential acetylation of Nrf2	MI rat model	Enhanced binding of Nrf2 to CBP/p300	[23]
Histone	Deacetylation of histone	DOX-induced cardiotoxicity in mice	Activation of Nrf2 and SIRT2 to inhibit myocardial apoptosis and oxidative stress	[103]
Histone	Deacetylation of histone	Cardiomyocytes <i>in vitro</i>	Enhanced activation of Nrf2 signaling by SIRT6	[60]
Nrf2 mRNA	miRNA-27a, -28a and -34a	MI rat model and Cardiomyocytes <i>in vitro</i>	Inhibition of Nrf2 translation in response to cardiac stress	[129,260]
Bach1 mRNA	miRNA-155-5p	Human Coronary Artery Endothelial Cells <i>in vitro</i>	Down-regulation of Bach1 potentially enhancing the cytoprotective response and preventing oxidative injury within infarct hearts	[132]
Keap1 mRNA	miRNA-7	Patients with MI and heart failure; human neuroblastoma cells	Inhibition of Keap1 expression and enhanced Nrf2 activity	[133,134]
Keap1 mRNA	miRNA-200a	Human cardiomyocytes; ischemic myocardial tissues; MI mouse model	Increased the nuclear translocation of Nrf2, and downstream target expressions	[135,136]
Nrf2 promoter	lncRNA <i>Sarrah</i>	Acute MI mouse model; Rat cardiomyocytes <i>in vitro</i>	Nrf2 activation mediating the cardioprotective effects of <i>Sarrah</i> , which involves the recruitment of CRIP2 and CBP/p300 to Nrf2 promoter	[155]
Nrf2 mRNA	LncRNA LINC00261	Rats I/R myocardial tissues and H/R-induced cardiomyocytes	LINC00261 acts as a sponge of miRNA-23b-3p to positively regulates Nrf2 expression in cardiomyocyte	[159]

Abbreviations: Transverse aortic constriction (TAC); Myocardial infarction (MI); Ischemia/reperfusion (I/R); hypoxia/reoxygenation (H/R); cysteine-rich protein 2 (CRIP2).

and ARE-dependent gene transcription by direct acetylation/deacetylation of either Nrf2 protein or in the promoter regions [52–54,89,90]. In addition to direct histone modifications of Nrf2 and ARE elements, other components of the Nrf2/ARE signaling pathway, such as Keap1 [91,92], HO-1 [89], SOD2 [93] and Gclc [94], can also be regulated by histone acetylation and methylation. While histone modifications of Nrf2/ARE have been well-documented and studied in various diseases, these modifications of Nrf2/ARE signaling in CV diseases, especially heart failure remain to be further elucidated. Epigenetic studies on humans with heart failure and in animal models have recently been reviewed [95], suggesting that histone acetylation/deacetylation are closely tied to cardiac hypertrophy. Interestingly, in a recent study from this laboratory we demonstrated that curcumin, a Nrf2 activator, enhances exercise capacity in heart failure by activating Nrf2 signaling and subsequently upregulating antioxidant defenses in skeletal muscle [29]. It has been reported that curcumin can prevent both the acetylation of histone (H3 and H4) and GATA4 DNA-binding activity by inhibiting CBP/p300 activity which is a well-known HAT and is upregulated in the myocardium in decompensated heart failure. Curcumin also prevents the interaction between CBP/p300 and GATA4 in cardiomyocytes, thus contributing to the prevention of cardiac hypertrophy and the development of chronic heart failure [80,96]. In a recent study from our laboratory we showed that systemic administration of bardoxolone methyl (CDDO-Me), another pharmacological activator of Nrf2, improves cardiac function in a rodent model of post MI chronic heart failure. Mechanistic studies revealed that CDDO-Me enhances the competitive binding of Nrf2 to CBP/p300 with NF- κ B by inducing both transcriptional and translational increase of Nrf2, resulting in the selective increase of Nrf2 targets and the attenuation of myocardial inflammation [23].

It has been well-documented that the Sirtuin family of proteins, including Sirtuin 1–7, which are class III histone deacetylases (HDACs) and are distributed in different subcellular compartments (Sirt 1, 2 in cytoplasm and nucleus; Sirt 3, 4, 5 in mitochondria and Sirt 6, 7 exclusively in the nucleus). The Sirtuins play important roles in protecting the heart against oxidative stress and myocardial inflammation in cardiovascular disease, including heart failure [97–101]. Recently, adiponectin, a unique adipocyte-derived cytokine has been shown to be cardio-protective [102]. The adiponectin agonist, ADP355 has been demonstrated to possess cardio-protective effects in Doxorubicin

(DOX)-induced cardiotoxicity by activating Nrf2 and Sirt 2 signaling pathways to inhibit myocardial apoptosis and oxidative stress [103]. This suggests that Sirt 2-mediated deacetylation of histones may enhance the binding of Nrf2 to ARE and the expression of downstream target genes. Sirt 6 plays an important role in the maintenance of cardiovascular homeostasis, especially in the preservation of cardiac function in response to stress [98,101,104]. Although Sirt 6-mediated cardio-protection depends on its deacetylase activity, Pan, et al. reported that Sirt 6 acts as a Nrf2 coactivator together with RNA polymerase II to transactivate Nrf2-regulated antioxidant genes, indicative of the importance of histone deacetylation for Nrf2 ARE-binding [59]. In addition, the Sirt6/Nrf2 axis is involved in the Forkhead box protein O6 (FOXO6)-regulated oxidative stress following MI. Down-regulation of FOXO6 can prevent hypoxic injury of cardiomyocytes through upregulating Sirt 6 to indirectly enhance Nrf2 activation [60]. Certainly, the regulatory functions of Sirt 6 on Nrf2/ARE signaling may be multi-faceted. Sirt 6 can also potentially promote Nrf2 activation by antagonizing the functions of Keap1 and Bach1, both Nrf2 natural inhibitors [104–106].

3.3. Non-coding RNA regulation of Nrf2/ARE signaling in heart failure

Non-coding RNAs (ncRNAs) including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) are emerging as key regulators of cellular homeostasis, and have high relevance to various human diseases, including CV disease. They have become promising therapeutic targets [107–112]. The regulation and functional roles of these ncRNAs in heart failure has been recently reviewed by Gomes et al. [113–115]. While the regulatory roles of miRNAs, lncRNAs and circRNAs in Nrf2 signaling have been well-documented in human disease [116–122], their regulatory functions in heart failure remains to be determined.

In 2009, Matkovich et al. performed a miRNA profile analysis of human myocardial specimens from heart failure patients with or without left ventricular assist devices (LVAD) compared to normal heart specimens. Myocardial miRNA profiles suggested that 28 miRNAs were significantly up-regulated in failing hearts [123]. Interestingly, 4 out of 28 heart failure miRNAs, including miRNA-24, -26, -27, and -103, have been implicated in cellular hypoxic responses [124], and 1 out of the 4 heart failure miRNAs, miRNA-27a, was identified in the

post-transcriptional control of Nrf2 expression and redox homeostasis in neuro-pathologies [125], diabetes [126] and liver diseases [127,128]. This miRNA was recently found by our laboratory to be upregulated in an animal model of chronic heart failure (post MI) and contributing to the dysregulation of Nrf2 protein [129]. In addition to miR-27a, we also demonstrated that miRNA-28a and -34a were dysregulated in the ischemic myocardium, further contributing to the down-regulation of Nrf2 protein through translational inhibition.

MiRNAs can also indirectly target other components of the Nrf2/ARE signaling pathway, such as Keap1 and Bach1 (BTB and CNC homolog1, DJ-1 (PAPK7, Parkinson protein 7). It has been well-documented that miRNAs, including miRNA let-7, miRNA-98 and miRNA-196, enhance Nrf2-target gene expression, such as HO-1 in hepatocytes [130,131], through the down-regulation of Bach1. Using Core-Shell Polymer-Based Nanoparticle technology, Antunes, et al. recently suggested that miR-155-5p can be delivered to endothelial cells and down-regulate Bach1 expression, potentially enhancing the cytoprotective response and preventing oxidative injury in infarcted hearts [132]. In addition, Xu, et al. performed a functional network analysis to investigate dysregulated miRNAs in myocardial infarction and heart failure. They showed that miR-7 plays a critical role in maintaining the dynamic balance of protein interactions in heart failure [133]. In a related study it was shown that miRNA-7 negatively regulates Keap1 expression resulting in enhanced Nrf2 activity [134]. In addition, miRNA-200a exerts protective effects on oxidative stress-induced cell death and inflammation in both the MI state and in diabetes by targeting Keap1-Nrf2 signaling [135,136]. MiRNA-122 also plays a central role in various CV diseases, including heart failure, hypertension, MI, atherosclerosis and atrial fibrillation [137]. The potential mechanisms involve the indirect deactivation of Nrf2 by miRNA-122 targeting Sirt1 and Sirt6, which enhance Nrf2 transcription by epigenetic regulation [59,60,138] (as illustrated in Fig. 2).

Long noncoding RNA (lncRNA, >200 bp) dysregulation has recently emerged as a mechanism for the modulation of Nrf2 signaling (as reviewed in Ref. [139]), while Nrf2 as a transcriptional factor also regulates the expression of several lncRNAs contributing to its cytoprotective effects as either transcriptional activators [140–143] or repressors [144]. These lncRNAs regulate Nrf2 signaling by different mechanisms including acting as miRNA sponges [145–149], histone acetylation [150], targeting Nrf2 inhibitors [151,152] and physical interaction with Nrf2 [153] as well as serving as a functional pseudogene to regulate Nrf2 targets [143]. While these lncRNAs have been involved in Nrf2 regulation in neurologic diseases [148,154], reproductive diseases [150], hepatic ischemia/reperfusion injury [147] and cancer [121,143,152,153], little research has focused on their regulation in heart failure.

Recent studies suggest that lncRNAs also contribute to the pathophysiology of heart failure through targeting Nrf2 signaling. Trembinski et al. [155] recently identified an aging-regulated lncRNA, designated as lncRNA *Sarrah*, which can protect cardiomyocytes from apoptosis after acute myocardial infarction. Using lncRNA *Sarrah* gain- and loss-of function strategies, this group observed that both transcriptional and translational regulation of Nrf2 were reduced after knockdown of lncRNA *Sarrah* by siRNAs. They further showed that *Sarrah* can directly bind to the promoter of genes that regulate chromatin remodeling by forming RNA-DNA-DNA triplex and subsequent gene activation and that Nrf2 was one of the targets mediating the cardioprotective effects of lncRNA *Sarrah*. This lncRNA also involves the recruitment of the cardiac transcription factor cysteine-rich protein 2 (CRIP2) and CBP/p300 to the Nrf2 promoter, suggesting the contribution of the lncRNA *Sarrah*-Nrf2 axis to cardiomyocyte survival following MI.

Another lncRNA, LINC00261 has been reported to suppress tumor progression by either sponging miRNAs or inhibiting the demethylation of the oncogene promoter [156–158]. Recently, this lncRNA was shown

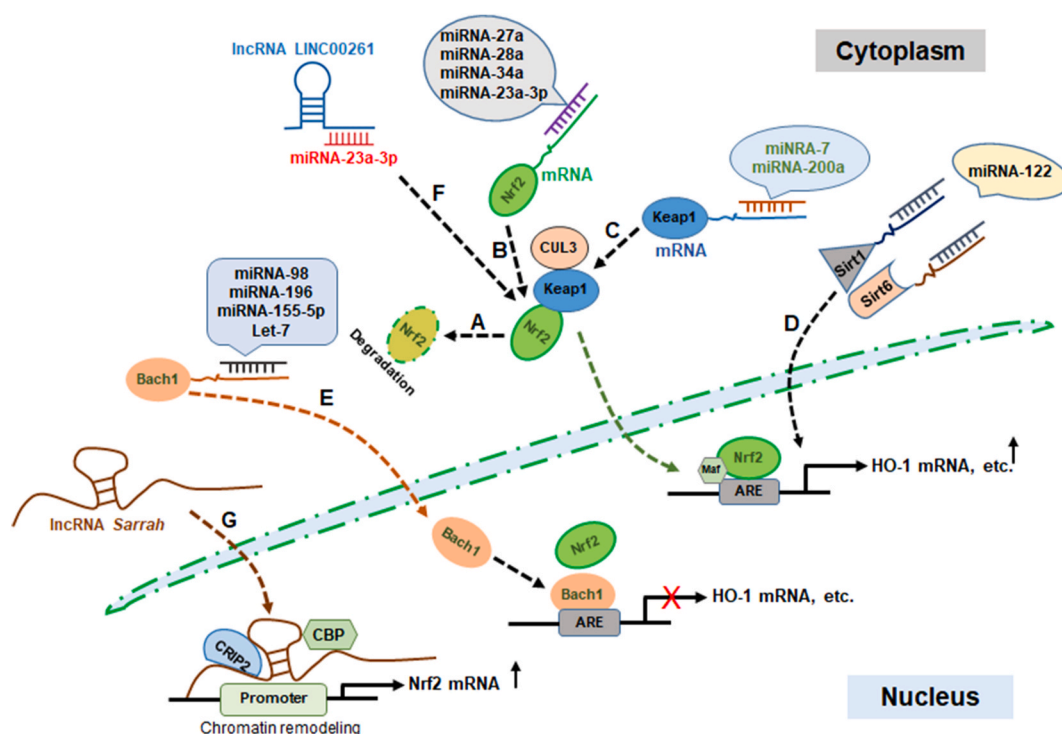


Fig. 2. Schematic diagram of epigenetic regulations of Nrf2 signaling by non-coding RNAs in the pathogenesis of heart failure. Keap1-dependent Nrf2 degradation in the normal condition (A); miRNAs inhibit Nrf2 signaling by directly inhibiting Nrf2 translation (B); miRNAs enhance Nrf2 signaling by indirectly inhibiting Keap1 translation (C); miRNA impacts Nrf2 signaling by inhibiting the translation of Nrf2 transcriptional enhancers (Sirt1/Sirt6) (D); miRNAs enhance Nrf2 signaling by inhibiting Bach1 translation (E); lncRNA LINC00261 enhances Nrf2 signaling by sponging miRNA-23a-3p (F); The recruitment of the cardiac transcription factor cysteine-rich protein 2 (CRIP2) and CBP/p300 by lncRNA *Sarrah* to the Nrf2 promoter for chromatin remodeling and Nrf2 transcriptional activation (G).

to be involved in ischemia/reperfusion (I/R)-mediated acute MI. Zhang et al. [159] demonstrated that the lncRNA LINC00261 protects cardiomyocytes from hypoxia/reoxygenation (H/R)-induced apoptosis by sponging miRNA-23a-3p to positively regulate Nrf2 expression. The potential roles of some non-coding RNAs in the regulating of the Nrf2/ARE signaling pathway in heart failure is illustrated in Fig. 2. However, their functions in heart failure still remain to be further elucidated.

The above discussion is preamble to the following assessment of the role played by myocardial derived extracellular vesicles (EVs) in transporting regulatory non-coding RNAs, proteins and other molecules that regulate oxidative stress through the Nrf2/Keap1 pathway in the heart and in remote tissues.

4. Extracellular vesicles, oxidative stress and chronic heart failure

Extracellular Vesicles have long been thought to be cell garbage, but are now emerging as important mediators of intercellular and intra-organ communication involved in various physiological and pathological processes in human diseases [160–163]. Based on their biogenic mechanisms, size range and vesicle components, EVs have been classified into two main categories, including ectosomes and exosomes. Ectosomes are further divided into different categories, including microvesicles, microparticles and large vesicles in the size range of 50–1000 nm in diameter. Exosomes are one type of endosomal small EV with a 40–150 nm size range. Exosomes can be secreted by most cell types and classified into classical- (CD63⁺, CD81⁺ and CD9⁺ expressing) and non-classic (CD63[−], CD81[−] and CD9[−]) exosomes (as reviewed in Refs. [164–166]). It has been well-known that proteins, genetic material, lipids and metabolites can be actively and selectively incorporated into EVs [167,168]. These EVs mediate intra- and inter-organ communication under normal and pathological conditions by shuttling their cargoes from donor to recipient cells and tissues.

4.1. Extracellular vesicles and cardiac remodeling in heart failure

While several soluble factors secreted by cardiac tissue including cytokines, chemokines and growth factors have been directly implicated in local inflammatory responses, oxidative stress and cardiac repair following MI in a growing number of studies have demonstrated that EVs have been shown to impact the pathogenesis of heart failure through local and remote communication mechanisms [169,170]. For instance, circulating angiotensin receptor 1 (AT1R)-enriched EVs released from the heart under cardiac stress likely modulate vascular responses to neurohormonal stimulation [171]. Myocardial infarction can significantly increase cardiac EV generation which, in turn, drive cardiac inflammation and remodeling by stimulating the innate immune system and cardiac monocyte infiltration. Recent studies suggest that large EVs, mainly secreted from cardiomyocytes and endothelial cells in the ischemic myocardium, were taken up by infiltrating monocytes resulting in an increase of pro-inflammatory cytokines and chemokines [169]. Interestingly, pro-inflammatory macrophages after MI also secrete EVs containing pro-inflammatory cytokines, including IL-1 α and IL-1 β which, in turn, contribute to cardiomyocyte toxicity and cardiac dysfunction through TLR4-dependent NF- κ B activation [172]. These events suggest a pathological role of EV proteins in heart failure.

It has been well-documented that circulating miRNAs are highly stable and actively transported by either binding to RNA-binding proteins resistant to nuclease degradation or entrapped in EVs [173–176]. Cardiac miRNA-enriched EVs secreted from cardiac fibroblasts have become a paracrine signaling mediator of cardiomyocyte hypertrophy through EV communication [177,178]. In addition to cardiac hypertrophy, EV components, such as non-coding RNAs, are involved in cardiac fibrosis following MI [179]. For example, EV-enriched miRNA-21 secreted by cardiomyocytes in response to cardiac stress, contributes to

cardiac fibrosis after myocardial ischemia through the activation of the AKT signaling pathway [180]. In addition, miRNA-30d has been used as a biomarker to predict left ventricular remodeling and clinical outcome in heart failure [181–183]. Recent mechanistic studies showed that miRNA-30d can not only inhibit autophagy-promoted ferroptosis in cardiomyocytes via binding to ATG5 after MI [184], but is also selectively overexpressed in cardiomyocytes in response to acute hypoxic stress and protects cells against MI-induced apoptosis through targeting mitogen-associate protein kinase (MAK4K4). Interestingly, miRNA-30d can be incorporated into cardiomyocyte-secreted EVs, further contributing to cardiac fibrosis by directly targeting integrin-5 α [185]. Recently, lncRNA-enriched EVs secreted by cardiomyocytes during cardiac hypoxia have also been found to contribute to cardiac fibrosis after MI [186]. These studies suggest a role for diagnostic, prognostic and therapeutic applications of EVs in heart failure.

4.2. Extracellular vesicles and Nrf2/ARE signaling in heart failure

A critical role for EVs has been demonstrated in redox-related processes by either producing ROS or eliminating ROS machinery [187]. The biogenesis of EVs can also be regulated by ROS [188,189]. Extracellular vesicles can carry ROS generating and ROS scavenging molecules to recipient cells to regulate the redox status of remote targets. For example, functional NADPH oxidase 2 (NOX2)-enriched EVs released from cytokine-recruited inflammatory macrophages mediate the regeneration of injured axons by ROS generation [190], and Nox2-enriched EVs can prevent immune processes associated with chronic inflammation and autoimmune diseases by inhibiting the proliferation CD4⁺ T cells once secreted by CD8⁺ regulatory T cells [191,192]. In addition to membrane bound Nox2, mitochondrial proteins, mitochondrial DNA and even free mitochondria which accumulates DAMPs such as TNF- α and ROS can mediate intercellular communications by EVs in human diseases, including cancer [193] and vascular inflammatory disease [194]. On the other hand, increasing evidence suggests that antioxidant proteins and small molecule ROS scavengers as well as the reductive power of NADPH can also be transferred by EVs to protect recipient cells against oxidative stress [195–198].

Important for this discussion, EVs are emerging as critical mediators for redox modulation in heart failure. For instance, circulating vesicular redox sensitive-miRNAs have been demonstrated to have a diagnostic, prognostic and therapeutic potential in heart failure patients [199]. It has been reported that circulating miRNA-1 is significantly increased in heart failure [123,200,201], contributing to cardiac oxidative stress by directly targeting SOD1, Gclc, and G6PD to increase ROS levels and susceptibility to oxidative stress in the myocardium [202]. In addition to miRNA-1, 27 miRNAs (miR-15a, -16, -22, -24, -26a, -26b, -27a, -29a, -29b, -30a-5p, -30b, -30c, -30d, -103, -125b, -126, -130a, -133b, -143, -195, -199a-3p, -378, -499, let-7f, let-7g, let-7i) have been identified to be significantly increased in heart failure patients. Importantly, these miRNA signatures in heart failure are reversed by left ventricular assist device (LVAD) implantation [123]. Bioinformatic analysis (TargetScanHuman 7.2) suggests that miRNA-27 including miRNA-27a-3p and miRNA-27b-3p, can directly target the 3' UTR of Nrf2 to inhibit the translation of Nrf2 mRNA. This is consistent with the above clinical findings in heart failure patients and has been validated in infarcted hearts of rats [129]. In addition, other miRNAs, including miR-155-5p [132], miRNA-7 [133,134], miRNA-200a [135,136], miRNA-28a and miRNA-34a [129] have been directly or indirectly involved in the regulation of Nrf2 translation in the pathogenesis of heart failure. Interestingly, studies from our laboratory demonstrated that three of these miRNAs, including miRNA-27a, -28-3p, and -34a, were highly expressed in the left ventricle of infarcted hearts. *In vitro* data suggest that these miRNAs can be preferentially incorporated into EVs in response to TNF- α stimulation, and secreted from cardiac cells to dysregulate Nrf2 translation in recipient cells by EV-mediated intercellular communication [129]. MiRNA-200a has been reported to

epigenetically inhibit Keap1 expression, indirectly activating Nrf2/ARE signaling to prevent hepatic fibrosis primarily due to a reduction in oxidative stress [203]. Interestingly, down-regulated miRNA-200a in EVs released from aged mesenchymal stem cells (MSC) contributes to the impairment of young MSC-EV-induced cardio-protective effects post MI [204], probably through restoration of Keap1 expression to significantly abrogate Nrf2 signaling-mediated cardio-protective effects.

Recently, miRNA-155-5p has been reported to induce vascular protection. Nanoparticle-loaded miRNA-155-5p was found to be cytoprotective in endothelial cells (ECs) and decreased injury in the infarcted heart [132]. Further mechanistic studies show that miRNA155-5p can be incorporated into EVs and secreted from fibroblasts and contribute to the proliferative inhibition of vascular smooth muscle cells by suppressing ACE expression [205]. Moreover, EV-miRNA-155 derived from macrophages is a paracrine regulator of fibroblast proliferation and inflammation in MI by targeting the Son of Sevenless 1 (Sos1) and Suppressor of Cytokine Signaling 1 (SOCS1) [206]. These studies suggest that EV-enriched miRNA-155 mediated intercellular communication contribute to cardio-protection through inhibition of Bach1 translation to indirectly enhance the Nrf2/HO-1 signaling pathway following MI. Interestingly, a recent study by Li et al. [207] suggested that EV Nrf2 protein secreted from Nrf2-overexpressing adipose-derived stem cells protects endothelial progenitor cells against high glucose-induced ROS generation and inflammatory cytokine expression. The latter promotes vascularization in a diabetic foot ulcer rat model, suggesting that this strategy may be therapeutic.

In addition to the involvement of EVs in the dysregulation of oxidative stress through Nrf2 signaling in the infarcted and failing heart through intercellular communication within the heart, EV-mediated inter-organ communications, especially heart-brain communication, may contribute to the pathogenesis of heart failure via regulating Nrf2 signaling. Mounting evidence has demonstrated a reciprocal crosstalk between the heart and brain [208,209]. On the one hand, brain injuries, such as stroke, may contribute to cardiac dysfunction by several mechanisms, including neurohormonal regulation, immune responses and inflammation [208]. On the other hand, a reciprocal relationship exists between the heart and brain in heart failure resulting in functional and anatomic abnormalities known as the cardio-cerebral syndrome [210–213]. While increased sympathetic outflow to the heart has been well established in heart failure [48,214–216], and this communication pathway is mediated primarily by discrete neural connections [217], increasing evidence suggest that cardiac-derived EVs following MI play important roles in brain injury. Sun et al. [209] reported that MI causes neuronal microtubular damage in the hippocampus through increased cardiac-derived miRNA-1 which circulates to the brain and targets brain-specific tubulin polymerization promoting protein (TPPP/p25). Our previous studies have demonstrated that sympatho-excitation in heart failure was attributed, in part, to central oxidative stress and reduced Nrf2 and antioxidant enzyme expression in the RVLM [30]. Selective deletion of Nrf2 in the RVLM mimicked this pathophysiological phenotype including elevated blood pressure, increased sympathetic outflow and impaired arterial baroreflex function [28]. Conversely, selective overexpression of Nrf2 in the RVLM attenuated sympatho-excitation in mice with chronic heart failure [30]. These studies suggest an important role for Nrf2 as a central target for autonomic modulation in heart failure, and suggest a heart-brain communication that involves Nrf2. In a recent study we showed that cardiac cells including cardiomyocytes and fibroblasts, can secrete Nrf2-targeting miRNA-enriched EVs in response to cardiac stress, and that these miRNAs contribute to dysregulation of Nrf2 signaling once taken up by recipient cells and contribute to pathological alterations, such as cardiomyocyte hypertrophy [129]. Given that Nrf2-targeting miRNA-enriched EVs are secreted into the extracellular space and circulate to sympatho-regulatory areas of the brain in diseases such as chronic heart failure, they are likely to contribute to the dysregulation of Nrf2 signaling in structures such as the RVLM and modulate oxidative

stress-mediated sympatho-excitation (Fig. 3). Thus, it remains to be further investigated if these cardiac-derived EV-enriched Nrf2-targeting miRNAs or other potential components contribute to the heart-brain crosstalk in the oxidative regulation of sympathetic outflow through targeting the Nrf2/Antioxidant signaling pathway.

5. Potential clinical applications and future perspectives

Given the potent effects of Nrf2 in cardiovascular disease, it is important to develop novel prognostic, diagnostic and therapeutic strategies for heart failure that rely on activation of this transcription factor. It has been well documented that the central renin angiotensin aldosterone system (RAAS) mediates, in part, sympatho-excitation in the setting of heart failure [218–220]. Recent studies from our laboratory suggest that selective activation of Nrf2 by sulforaphane (a natural isothiocyanate derived from cruciferous vegetables) in the RVLM can attenuate the central Ang II-induced pressor response by upregulating Nrf2-downstream antioxidant enzymes [221]. Activation of Nrf2 in skeletal muscle of mice with heart failure with low ejection fraction (HFrEF) by curcumin improves exercise capacity in heart failure [29]. These findings suggest a promising therapeutic strategy impacting exercise tolerance and the quality of life in HFrEF patients. Furthermore, mechanistic studies have shown that sulforaphane not only promotes the dissociation of Nrf2 from Keap1 by modifying the sulfhydryl groups of Keap1 [222], but also enhances Nrf2 expression by regulating the methylation and acetylation status at the Nrf2 promoter (reviewed in Ref. [119]). In addition, curcumin-induced Nrf2 signaling activation has been attributed to the demethylation of CpG islands in the Nrf2 promoter by inhibiting the activity of DNA methyltransferases [223]. Recently, we investigated the effects of bardoxolone methyl, a pharmacological activator of Nrf2, in a rodent model of heart failure and observed that short-term systemic administration of bardoxolone methyl exhibited beneficial effects on cardiac function, including increased cardiac output and stroke volume and decreased left ventricle end-diastolic pressure. Molecular studies further suggest that bardoxolone methyl regulates Nrf2 signaling by either modifying Keap1 to release Nrf2 and translocation to the nucleus where Nrf2 competitively binds to the Creb binding protein (CBP) with NF- κ B, or directly inhibits I κ B activity resulting in a reduction of I κ B phosphorylation and subsequent cytosolic sequestration of NF- κ B, both contributing to enhanced antioxidant enzyme transcription and attenuated myocardial inflammation in injured myocardium [23]. These studies suggest that small molecule Nrf2 activators provide a promising therapeutic strategy for the treatment of heart failure. It has been well-documented that Nrf2 activation mediated by small molecule activators contributes to cardio-protection by multiple mechanisms including disruption of Keap1-mediated Nrf2 ubiquitination, promoting autophagic degradation of Keap1, and metabolic regulation [224–226]. Pharmacological activators of Nrf2 have been used clinically for the treatment of oxidative stress-related chronic inflammatory diseases including diabetes, neurodegenerative disorders, cardiovascular diseases and renal disease [227]. The cardio-protective effects of Nrf2 signaling appears to be dependent on the integrity of myocardial autophagy during cardiac remodeling. Qin et al. reported that functional autophagy switches on Jak2/Fyn signaling to mediate Nrf2 nuclear export and subsequent degradation. Once cell autophagic function is impaired during pressure overload, abnormal nuclear accumulation of Nrf2 contributes to maladaptive cardiac remodeling and heart failure through direct Nrf2-mediated overexpression of angiotensinogen [49]. This may explain why patients with diabetic renal disease clinically treated with bardoxolone methyl are prone to heart failure. This finding directly led to the early termination of clinical trials of bardoxolone methyl [228,229]. It is likely that small molecule Nrf2 activators have broad applications in the clinical treatment of heart failure, but not without potential complications. Importantly, the concept of reductive stress (RS) is also attracting attention by the scientific community. RS is defined as excessive

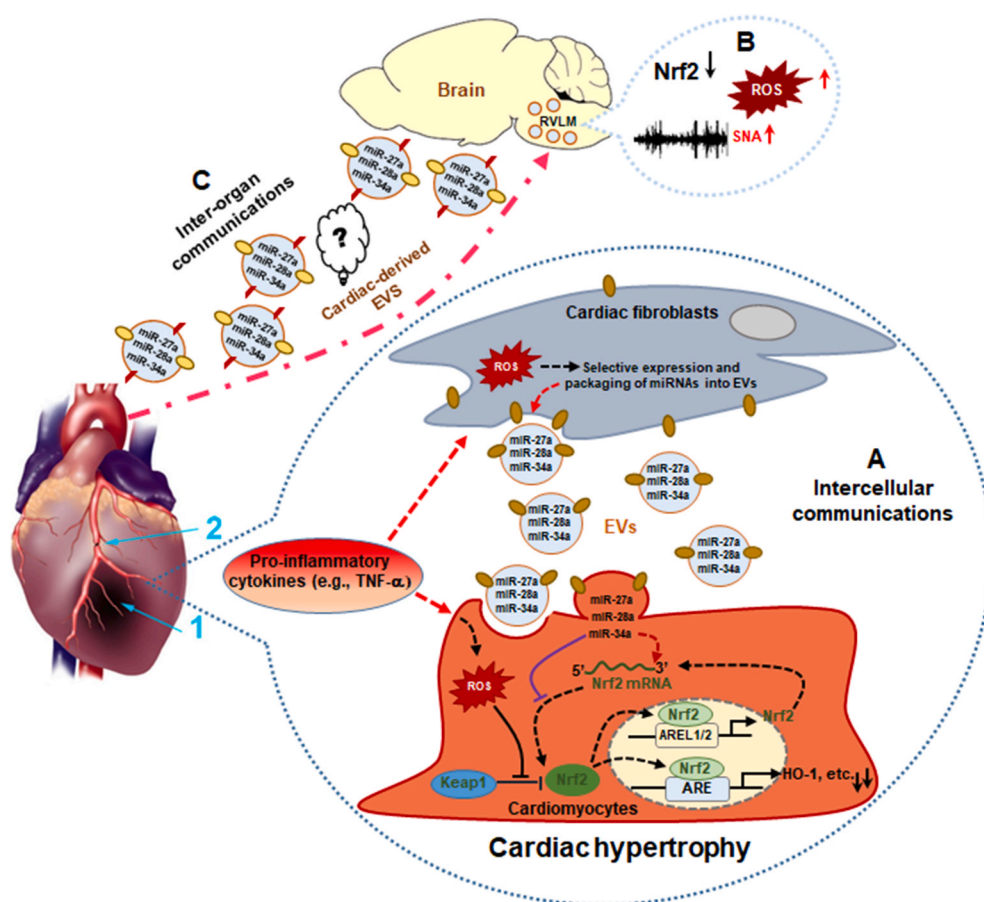


Fig. 3. MI-induced cardiac-derived EVs potentially regulate myocardial and brain Nrf2 signaling pathways by intra- and inter-organ communication. Under cardiac stress, fibroblast-derived EVs with miRNAs targeting Nrf2 mRNA inhibits Nrf2 translation in cardiomyocytes contributing to the dysregulation of antioxidant genes during MI (A); Nrf2 signaling was dysregulated in the rostral ventrolateral medulla (RVLM) in rats with heart failure, contributing to the increased ROS and sympathetic nerve activity (SNA) (B); Circulating cardiac-derived EVs may potentially mediate heart-brain communication through targeting brain the Nrf2 signaling pathway in heart failure (C); 1: Myocardial Infarction (MI); 2: Ligation of Left Anterior Descending (LAD) coronary artery.

antioxidant production in the presence of an intact redox system. Chronic RS can induce oxidative stress, which in turn, feeds forward to amplify RS [230,231]. Increasing evidence [63,231–233] shows that constitutive activation of Nrf2 signaling can cause RS which will drive pathological cardiomyopathy with diastolic dysfunction, leading to heart failure. Nrf2 deficiency will attenuate the RS-induced pathological phenotypes. These studies suggest that Nrf2 activity needs to be maintained at optimal levels so that abnormal activation of Nrf2 does not contribute to either oxidative stress or reductive stress contributing to the pathogenesis of heart failure.

Circulating miRNAs are emerging as promising biomarkers for various diseases, including heart failure. Clinical and animal studies have demonstrated the possibility that altered circulating miRNA profiling can serve as a diagnostic and prognostic test in end-stage cardiomyopathy and heart failure patients [123,234,235]. Oxidative stress associated miRNAs have been linked to the progression of heart failure and show therapeutic potential for heart failure (reviewed in Ref. [199]). Importantly, some miRNAs that target the Nrf2 signaling pathway, also show significant alteration in the plasma of patients with coronary artery disease. These include miRNA-155 [236] and miRNA-27a [237]. Increased levels of circulating miRNA-27a has also been used to predict clinical outcomes from acute MI [238], consistent with the alterations of miRNA-27a seen in patients with failing hearts [123]. Accumulating evidence supports the view that EVs are major vehicles for circulating miRNAs protected from circulating ribonuclease [239]. Previous studies from this laboratory also demonstrated EV-mediated intercellular communication by which miRNAs that target Nrf2 dysregulate Nrf2 expression in heart failure [129], supporting the possibility that EV-enriched Nrf2-targeting miRNAs may be used as prognostic and diagnostic markers for MI and heart failure.

In addition to EV-mediated intercellular communications within

heart, different tissues also communicate with each other by various signals, (e.g. bioactive molecules) delivered by EVs to maintain homeostasis and adapt to external conditions [240,241]. Heart failure is associated with brain injury/dysfunction including anatomic and physiological alterations (reviewed in Ref. [213]). It has recently been demonstrated that cardiac dysfunction contributes to brain structural changes by altering gray matter density (GMD) [211]. These investigators concluded that ejection fraction is positively correlated with regional GMD. Although neurohormonal regulation is believed to contribute to heart-brain crosstalk in the setting of heart failure, mounting evidence suggests that EVs and their cargoes, can act as mediators of this communication pathway. For example, cardiac-derived miRNA-1 has been implicated in MI-induced neuronal damage in the mouse hippocampus [209]. Transgenic overexpression of miRNA-1 in the mouse heart attenuates hippocampal synaptic vesicle exocytosis through miRNA-1-enriched EV-mediated translational inhibition of SNAP-25, whereas stereotaxic injection of a miRNA inhibitor into the hippocampus significantly ameliorates MI-induced deficits in hippocampal long-term potentiation (LTP) [242,243]. Given that MI can induce Nrf2-targeting miRNA-enriched EV secretion from cardiac cells, and Nrf2 signaling dysregulation and sympatho-excitation were observed in sympathetic regulatory areas of the brain in heart failure, it will be of interest to determine if cardiac-derived miRNA-enriched EVs mediate dysregulation of Nrf2 signaling and subsequent oxidative stress, inflammation and sympatho-excitation in heart failure patients. Certainly, important concerns about the role of miRNAs contained in EVs in heart-brain interaction still remain to be addressed. These include the following questions: How do alterations in oxidative stress-associated miRNAs, especially those related to the Nrf2 signaling pathway, in the heart affect autonomic function? Can these Nrf2 signaling-related microRNAs be used to differentiate preserved (HFpEF)

from reduced ejection fraction heart failure (HFrEF)? While circulating miRNA signatures have shown the potential to improve the diagnosis of heart failure and to differentiate between HFpEF and HFrEF [244,245], the combination of circulating miRNAs including EV-enriched miRNAs and natriuretic peptides, will warrant the maximal diagnostic accuracy [246,247]. How do cardiac-derived EVs distribute to specific brain regions? Does the expression profile of circulating and cardiac-derived EVs correspond to disease stages in heart failure? Because Nrf2 signaling also has anti-inflammatory functions, do cardiac-derived EV-enriched miRNAs affect central function and structure and infiltrating inflammatory cells indirectly secreted from brain EVs and their cargoes? Further studies are warranted to elucidate the role of intercellular communication in facilitating interaction between the heart and brain in the progression of heart failure.

Moreover, circulating miRNA-enriched EVs are not only used as prognostic and diagnostic biomarkers for heart failure, but may also be developed into new therapeutic strategies for heart failure. In particular, EVs as therapeutic tools may have potential to regulate the Nrf2 signaling pathway. Overexpressing Nrf2 in adipose-derived stem cells (ADSCs) may increase Nrf2-enriched EV secretion, which can promote increased vascularization, decrease in inflammation and oxidative stress in the progression of wound healing [207]. Similarly, platelet-derived exosomes also promote wound healing through YAP activation [248]. The interactions between Nrf2, Pix2 and YAP have been proposed to maintain the antioxidant response during cardiac repair after injury [249], suggesting that Nrf2 may also be involved in the platelet-derived EVs mediated protective effects. Small molecule Nrf2 activators, such as curcumin, have been encapsulated into EVs enhancing tissue bioavailability and efficacy [250,251], and has been used for the treatment of oxidative stress-related and inflammatory diseases [252,253]. In a recent preclinical study Cai et al. demonstrated the therapeutic potential of EVs carrying miRNA inhibitors (antagomirs) for ischemia-reperfusion-induced lung injury [254], suggesting the possibility of restoring Nrf2 signaling by EV-enriched antagomirs targeting Nrf2-related miRNAs. The use of EVs as delivery tools to treat heart failure still faces some challenges, especially insufficient targeting capabilities. Recent research in engineering modifications of EVs provide a new direction for EV-mediated therapeutic strategies in heart failure. Extracellular vesicle membrane surfaces engineered with either directly embedded tissue-specific antibodies or homing peptides *ex vivo* can enhance vesicle uptake in cells of interest [255]. For instance, EVs engineered with cyclo (Arg-Gly-Asp-D-Tyr-Lys) peptide (c(RGDYK)) peptide efficiently target lesions in the ischemic brain [256]. Extracellular vesicles engineered with rabies viral glycoprotein (RVG) peptide specifically bind in the central nervous system using the acetylcholine receptor [257]. Ischemic myocardial-targeting peptide CSTSMLKAC (IMTP) and cardiac homing peptide (CHP) were found to enhance the specificity of EV targeting ischemic myocardium as a therapeutic for MI [258,259]. Strategies of this type can be used to target the Nrf2 signaling pathway in CV diseases.

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