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REVIEW

The Nrf Family and Its Cardioprotective Potential: Mechanisms, Functions, and Therapeutic Perspectives

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Abstract: This review systematically elucidates the molecular mechanisms and therapeutic potential of nuclear factor erythroid 2-related factor (Nrf) family members in the cardiovascular system. As critical components of the CNC-bZIP transcription factor family, the Nrf family (including Nrf-2/NFE2L2, Nrf-1/NFE2L1, and Nrf-3/NFE2L3) orchestrates antioxidant response element (ARE)-dependent gene expression networks, playing pivotal roles in maintaining redox homeostasis, modulating inflammatory responses, improving mitochondrial function, and regulating programmed cell death (apoptosis, autophagy, and pyroptosis). Clinical data have demonstrated that in patients with myocardial infarction, the expression of Nrf-3 gene is significantly upregulated in myocardial cells within the infarcted area. Its high expression is associated with increased in-hospital mortality during the acute phase and accelerated progression of ventricular remodeling. Knockout of the Nrf-3 gene can reduce the acute-phase mortality of myocardial infarction, improve ventricular remodeling, and enhance cardiac function. Additionally, a crossover trial involving 19 participants showed that after 2 months of administration of olive oil by-product pâté tablets, the plasma Nrf-2 level in the subjects increased by 88.9% with concurrent improvement in cardiovascular risk factors. Collectively, these findings confirm the impact of the Nrf family on cardiovascular prognosis and its potential for intervention. Furthermore, we comprehensively analyze the regulatory functions of Nrf members in major cardiovascular pathologies, including myocardial ischemia-reperfusion injury, atherosclerotic plaque formation/stabilization, and heart failure progression. Based on recent advances, we also discuss innovative therapeutic strategies targeting the Nrf pathway, encompassing pharmacological activators, gene/epigenetic therapies, combinatorial approaches, and lifestyle interventions, thereby providing a theoretical framework and novel perspectives for the precision medicine of cardiovascular diseases.

Keywords: Nrf family, cardioprotection, oxidative stress, inflammation, mitochondria, programmed cell death

Introduction

The Nrf family, a pivotal subgroup of the CNC-bZIP transcription factors, serves as a master regulator of cellular oxidative stress, inflammatory responses, mitochondrial function, and programmed cell death (including apoptosis, autophagy, and pyroptosis). These processes are essential for maintaining cardiovascular homeostasis.[1] Comprising three principal members—Nrf-2 (encoded by NFE2L2), Nrf-1 (NFE2L1), and Nrf-3 (NFE2L3)—the Nrf family exhibits distinct yet interconnected roles in cardiovascular pathophysiology. Notably, Nrf-2 has emerged as a central focus in cardiac research due to its pleiotropic regulatory effects in myocardial ischemia-reperfusion injury, atherosclerosis, heart failure, and other cardiovascular disorders.[2]

CVDs, the leading global cause of mortality and disability, represent a paramount challenge in medical research due to their multifactorial pathogenesis and therapeutic complexity. These conditions not only pose severe threats to human health but also impose substantial socioeconomic burdens worldwide.[3] Given the pivotal role of the Nrf family in

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orchestrating cellular redox homeostasis, inflammatory modulation, and metabolic regulation, elucidating the structural and functional characteristics of Nrf members and their mechanistic contributions to CVDs pathogenesis holds transformative potential for developing novel therapeutic strategies.[4]

This article aims to review the basic structure and functional characteristics of the Nrf family, systematically expound its complex mechanism of action in CVDs, and summarize the potential cardiovascular treatment strategies targeting the Nrf family. By comprehensively analyzing the protective mechanisms of the Nrf family in cardiac health, we expect to provide new ideas and directions for the treatment of CVDs and promote the in-depth development of research in this field.

Overview of the Nrf Family

The Nrf family belongs to the CNC-bZIP transcriptional activator family, and its members include Nrf-2 (NFE2L2), Nrf-1 (NFE2L1), Nrf-3 (NFE2L3), etc. These members exhibit structural similarities and all contain specific functional domains, such as Neh1-7 and so on. The members of the Nrf family bind to Keap1 in the cytoplasm and remain in an inert state. Under stress conditions such as oxidative stress, the Nrf family members decouple from Keap1, translocate into the nucleus, form heterodimers with Maf proteins, bind to the ARE, and activate the expression of antioxidant genes and Phase II detoxifying enzymes, thereby exerting antioxidant stress and anti-inflammatory effects.

Basic Structure and Function of Nrf-2

Domain Composition and Molecular Characteristics

Nrf-2 (NFE2L2) belongs to the CNC-bZIP transcription factor family. Its highly conserved molecular structure and functional domain organization make it a core regulatory hub for cellular redox homeostasis (Figure 1).[5] The Nrf-2 protein is composed of seven evolutionarily conserved Neh (Nrf-2-ECH homology) functional domains (Neh1-Neh7). Each domain collaboratively senses oxidative stress signals, undergoes nuclear translocation, and activates the transcription of target genes.[6] Among them, the Neh1 domain is located at the C-terminus. As a bZIP module, it mediates the formation of heterodimers between Nrf-2 and proteins such as sMaf, and initiates the transcription of downstream genes

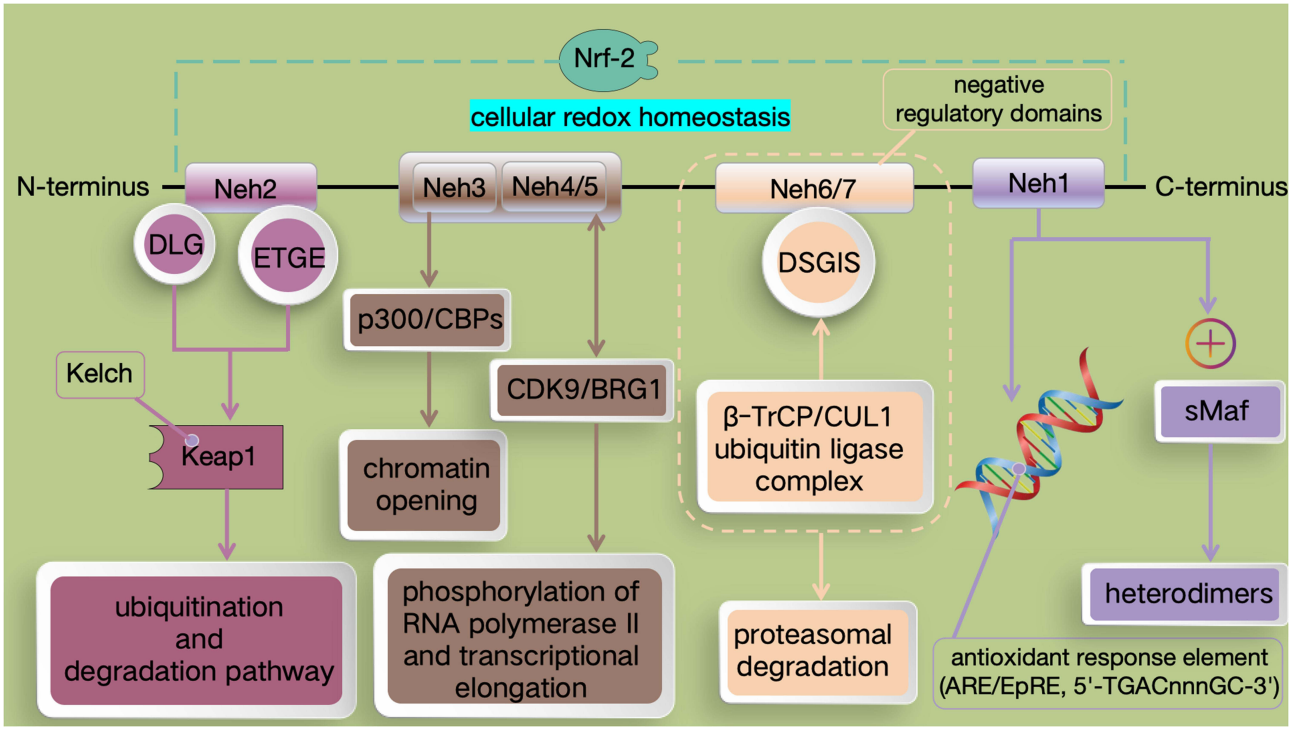

Figure 1 The Molecular Basis of the Neh Functional Domains of Nrf-2 and Oxidative Stress Signal Transduction.

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by specifically recognizing the antioxidant response element (ARE/EpRE, 5'-TGACnnnGC-3') on DNA. The Neh2 domain is located at the N-terminus and contains two key motifs, DLG and ETGE, which bind to the Kelch domain of Keap1 and participate in the regulation of the Keap1-dependent ubiquitination and degradation pathway.[7,8] The Neh3-5 domains together form a TAD: Neh3 promotes chromatin opening by recruiting histone acetyltransferases such as p300/CBP, while Neh4/5 interacts with the CDK9/BRG1 complex to drive the phosphorylation of RNA polymerase II and transcriptional elongation.[9,10] In addition, Neh6/7 serve as negative regulatory domains. The DSGIS motif in them can be recognized by the β-TrCP/CUL1 ubiquitin ligase complex, mediating phosphorylation-dependent proteasomal degradation, thereby restricting Nrf-2 activity under oxidative stress-independent conditions.[11]

Dynamic Regulatory Network

The dynamic regulation of Nrf-2 is mediated by a multi-level molecular network, which encompasses mechanisms such as ubiquitination and degradation, kinase phosphorylation, epigenetic modification, and regulation by non-coding RNAs. These mechanisms constitute an accurate two-way equilibrium system.[12] This network not only maintains redox homeostasis but also participates in cardioprotective pathological interventions through spatiotemporal-specific regulation, providing potential targets for the precise treatment of CVDs (Figure 2).

Under physiological homeostasis, the activity of Nrf-2 is strictly regulated by the Keap1-CUL3 E3 ubiquitin ligase complex. Keap1 specifically recognizes the ETGE and DLG motifs of Nrf-2 through its Kelch domain (β-helical barrel conformation), forming a Keap1-Nrf-2-CUL3 ternary complex with a 1: 2 binding mode.[13] The Cys151, Cys273, and Cys288 residues within the BTB domain of Keap1 constitute redox-sensitive sites, which can be covalently modified by ROS, electrophilic compounds (such as sulforaphane), or endogenous lipid peroxidation products (4-HNE), triggering a conformational change and releasing Nrf-2.[14] In the basal state, after Nrf-2 binds to Keap1 through the Neh2 domain, it is rapidly degraded via the CUL3-mediated ubiquitination-proteasome pathway (with a half-life of approximately 20 minutes), thus maintaining a low-level steady state in the cytoplasm.

Under pathological conditions, oxidative stress dynamically regulates the nucleocytoplasmic shuttling and stability of Nrf-2 through kinase cascade reactions.[15] In terms of positive regulation, PKCδ promotes the dissociation of Nrf-2 from Keap1 and enhances the efficiency of nuclear translocation by phosphorylating the Ser40 site of Nrf-2; the MAPK family

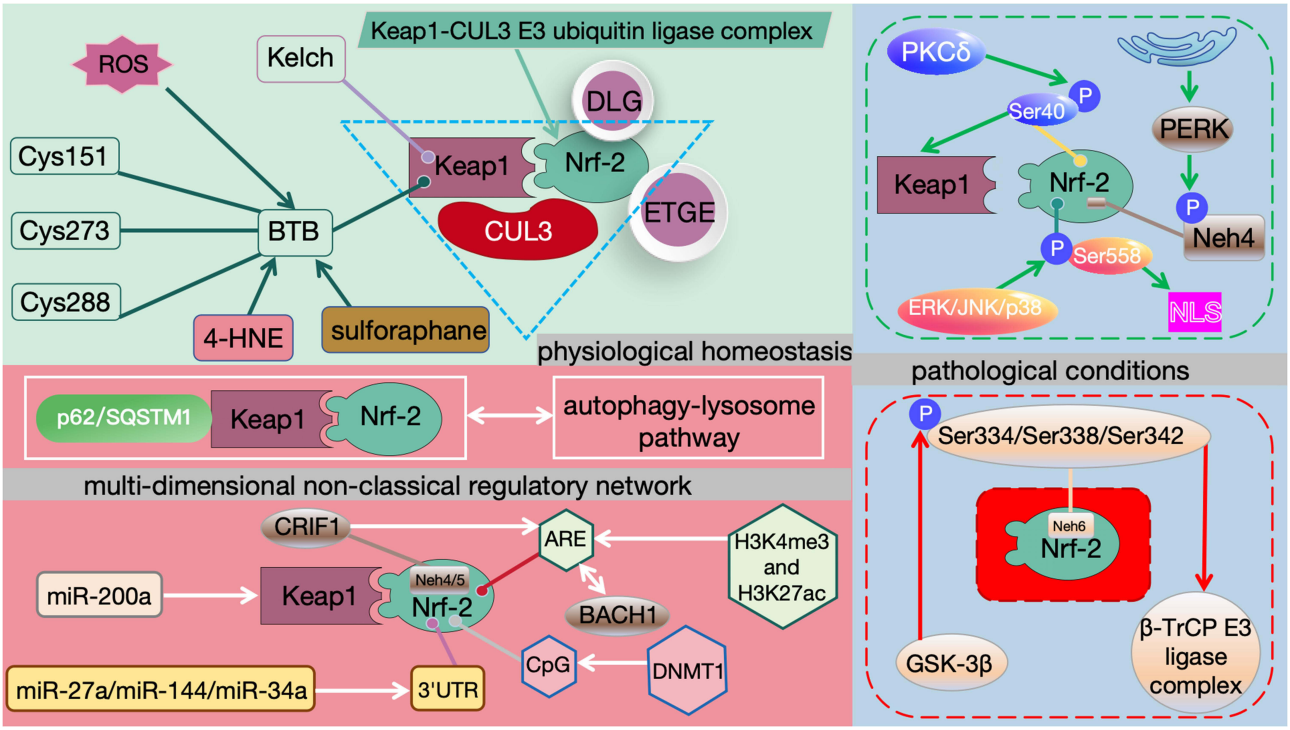

Figure 2 The Multilayer Molecular Network of the Dynamic Regulation of Nrf-2 and Its Cardioprotective Effects.

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(ERK/JNK/p38) stabilizes the NLS of Nrf-2 by phosphorylating the Ser558 site; PERK activated by endoplasmic reticulum stress synergistically enhances its transcriptional activity by phosphorylating the Neh5 domain. In contrast, GSK-3β recruits the β-TrCP E3 ligase complex by phosphorylating the Neh6 domain (Ser334/Ser338/Ser342), driving the proteasomal degradation of Nrf-2 and forming a negative feedback regulation mechanism. This two-way kinase regulatory network ensures the precise spatiotemporal regulation of Nrf-2 activity under oxidative stress conditions.

The dynamic balance of Nrf-2 is also precisely regulated by a multi-dimensional non-classical regulatory network. The autophagy-lysosome pathway competitively binds to Keap1 through the KIR domain of p62/SQSTM1 to form a p62-Keap1-Nrf-2 ternary complex, which promotes the degradation of Keap1 via LC3-II-labeled autophagosomes, thus releasing Nrf-2 into the nucleus.[16] At the epigenetic level, the hypermethylation of the CpG island in the promoter region of Nrf-2 mediated by DNMT1 inhibits its transcription, while the enrichment of histone active modifications such as H3K4me3 and H3K27ac in the ARE region enhances its transcriptional activity.[17] The microRNA network achieves post-transcriptional regulation by targeting the 3'UTR of Nrf-2 mRNA through miR-27a/miR-144/miR-34a. Meanwhile, oxidative stress relieves the inhibition of Keap1 mRNA by downregulating miR-200a. In the nucleus, CRIF1 inhibits the binding of Nrf-2 to ARE by binding to the Neh4/Neh5 domains of Nrf-2, while BACH1 competitively occupies the ARE sites, forming a dynamic antagonistic balance with Nrf-2, jointly constituting a complex regulatory system.[18]

Cardiovascular Protection Mechanisms and Challenges

In the cardiovascular system, Nrf-2 exerts a protective effect through a multi-target synergistic mechanism (Figure 3).[19] Its core functions include: (1) Activating antioxidant enzymes such as HO-1, NQO1, GCLC/GCLM, and GPX4, maintaining the GSH pool and SLC7A11 expression, and reducing the oxidative burst and ferroptosis during ischemia-reperfusion injury;[20] (2) Inhibiting the nuclear translocation of the NF-κB signaling pathway and the assembly of the NLRP3 inflammasome, down-regulating the secretion of pro-inflammatory factors such as IL-6 and TNF-α, and simultaneously blocking the TGF-β/Smad3 pathway to inhibit the activation of cardiac fibroblasts and collagen deposition;[21,22] (3) Up-regulating mitochondrial biogenesis-related genes such as TFAM and NDUFV1 through the PGC-1α-dependent pathway, promoting mitophagy driven by the p62-Keap1-Nrf-2 positive feedback loop, and coordinating the metabolic reprogramming of glycolysis (GLUT1, HK2) and fatty acid oxidation (CPT1A, ACADL) to meet

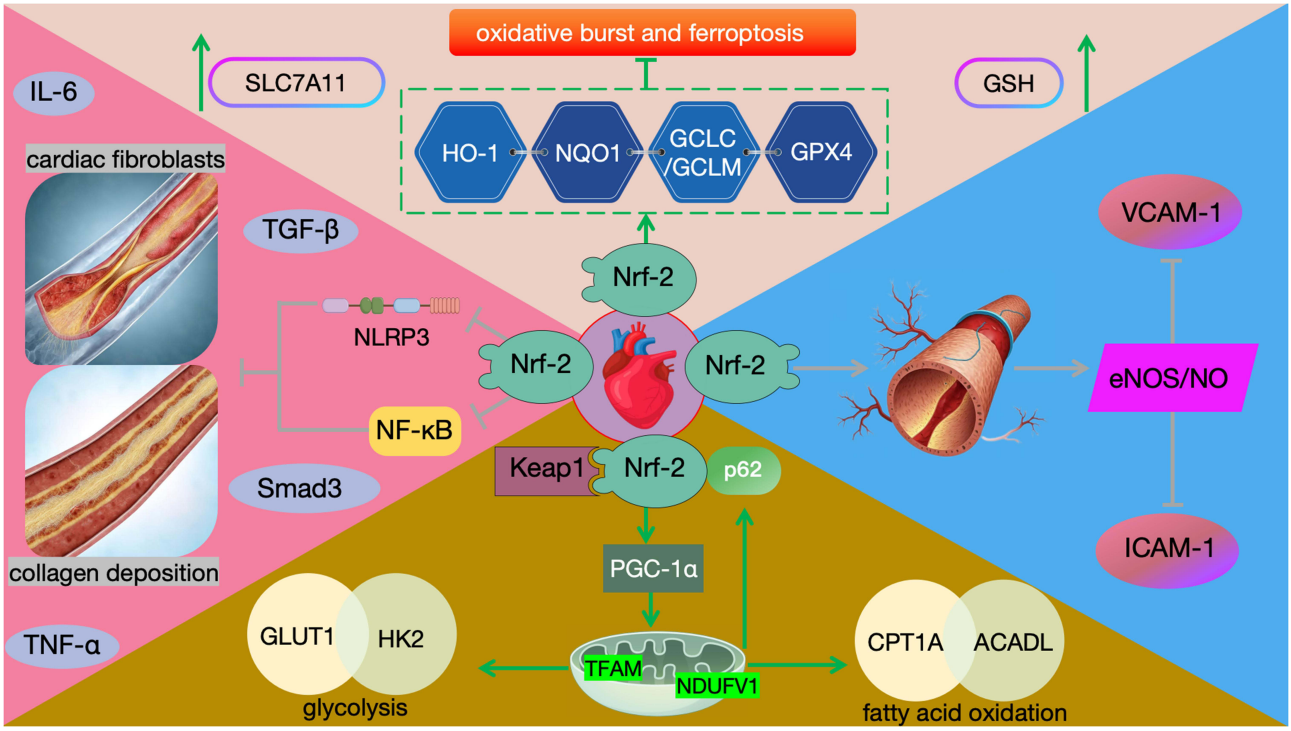

Figure 3 The Mechanism of the Synergistic Action of Multiple Targets of Nrf-2 in Cardioprotection.

the energy demands;[23] (4) Enhancing the function of vascular endothelium, inhibiting the expression of VCAM-1/ICAM-1 through the eNOS/NO axis, reducing monocyte infiltration and the formation of atherosclerotic plaques.[24]

Although Nrf-2 agonists such as sulforaphane and CDDO-Me have demonstrated significant cardioprotective potential in preclinical studies, their translational application still faces the challenge of dual effects. Chronic activation of Nrf-2 may promote tumor progression through Warburg effect-like metabolic reprogramming, and its cross-regulation with pathways such as IRF1/GPX4, PI3K/Akt, and Wnt/β-catenin may lead to off-target effects.[25,26] The latest research shows that exosome-like nanovesicles derived from tomatoes can significantly reduce restenosis after vascular injury through the Keap1/Nrf-2 signaling pathway.[27] The mechanism of action involves the inhibition of neointimal hyperplasia mediated by miRNA164a/b-5p. This nanovesicle can effectively inhibit the proliferation, migration, and phenotypic transformation of vascular smooth muscle cells, and at the same time upregulate the expression of antioxidant genes, thereby significantly improving the state of oxidative stress. Current research focuses on developing a myocardial-targeted nanodelivery system to achieve tissue-specific activation, and exploring combination strategies such as dual pathway inhibitors of Nrf-2/NF-κB to optimize the therapeutic window.

Basic Structure and Function of Nrf-1

Nuclear factor E2-related factor 1 (Nrf-1, NFE2L1), as an important member of the CNC-bZIP transcription factor family, although it shares structural homology with Nrf-2, its subcellular localization, activation mechanism, and biological functions exhibit significant specificity.[28] Nrf-1 is anchored to the endoplasmic reticulum membrane in the form of a transmembrane protein. Its N-terminus contains a hydrophobic signal peptide and a glycosylation modification site, while the C-terminus retains the conserved bZIP domain (Neh1).[29] Unlike Nrf-2, the regulation of Nrf-1 activity does not rely on Keap1-mediated ubiquitination and degradation, but rather achieves a dynamic balance through the endoplasmic reticulum-associated degradation pathway. Under conditions of endoplasmic reticulum stress, the precursor of Nrf-1 (p120) is processed by the proteasome to generate the mature form (p95/p85). The latter translocates into the nucleus, forms a heterodimer with MafG/K proteins through the Neh1 domain, binds to the antioxidant response element or the GC box (5'-GCTGAGTCAT-3') in the promoter region of target genes, and activates the transcription of genes related to mitochondrial biogenesis, oxidative phosphorylation, and lipid metabolism (Figure 4).[30]

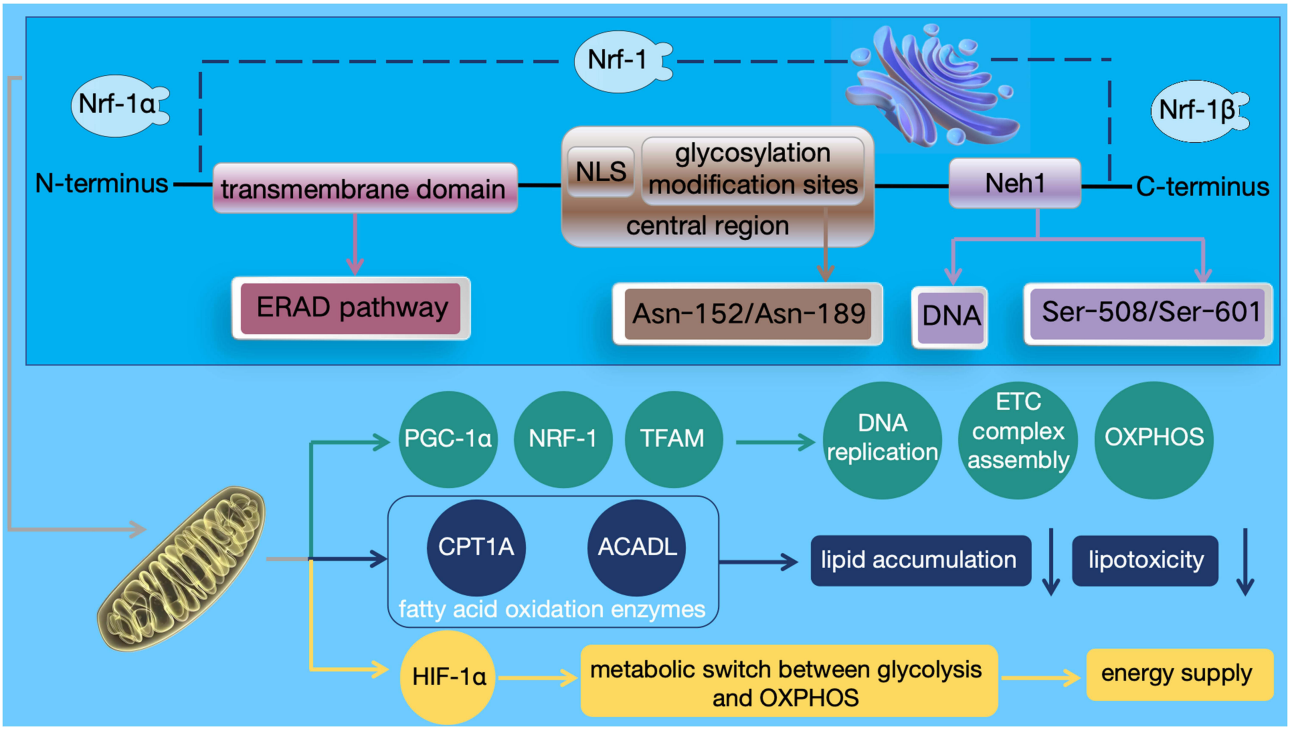

Figure 4 Structural Characteristics, Functional Mechanisms of Nrf-1 and Its Double-edged Sword Effect in the Cardiovascular System.

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The functional domain organization of Nrf-1 contains multiple regulatory modules: Its N-terminal transmembrane domain not only mediates the localization to the endoplasmic reticulum but also participates in the proteasomal processing of the ERAD pathway. The central region contains a NLS and glycosylation modification sites (Asn-152/Asn-189), and the latter affects the nuclear translocation efficiency by regulating protein stability. In addition to being responsible for DNA binding, the C-terminal bZIP domain (Neh1) also regulates transcriptional activity through phosphorylation modifications (such as Ser-508/Ser-601).[31] It is worth noting that Nrf-1 has multiple splicing isoforms (such as Nrf-1α, Nrf-1β), and the tissue-specific expression and functional differences of these isoforms may explain its unique role in the heart.[32]

Nrf-1 plays a crucial role in the process of cardiac regeneration in neonatal mice.[33] After cardiac injury, cardiomyocytes enter the cell cycle. At this time, Nrf-1 acts in concert with the nuclear transcription factor Y subunit α, performing the functions of protection and promoting proliferation respectively. In the non-regenerative hearts of mature mice, the overexpression of Nrf-1 can effectively protect the heart from ischemic injury and cardiomyocytes from doxorubicin-induced cardiotoxicity by upregulating genes related to the ERAD pathway. This finding further deepens our understanding of the cellular basis of neonatal cardiac regeneration. Furthermore, the stress response mechanism mediated by Nrf-1 is essential for neonatal cardiac regeneration and also provides protection for the adult heart. However, the pathophysiological significance of Nrf-1 in vascular diseases is two-sided. In adults, the overexpression of Nrf-1 may exacerbate atherosclerosis, but it can also prevent or mitigate myocardial ischemia-reperfusion injury. Specifically, studies have confirmed that in the lipopolysaccharide-treated mouse model, Nrf-1 negatively regulates the transcriptional processing of TRIM59 through the JNK signaling pathway, which may promote the progression of inflammation and atherosclerosis.[34] In contrast, in myocardial ischemia-reperfusion injury, Nrf-1 exerts a cytoprotective function on cardiomyocytes by inducing a dual stress response, including the inhibition of proteasome stress and the maintenance of redox balance.[35]

In the cardiovascular system, Nrf-1 maintains mitochondrial homeostasis and energy metabolism through a multi-level network.[32,36] Its core mechanisms include: (1) Directly regulating genes such as PGC-1α, NRF-1, and TFAM, driving mitochondrial DNA replication, the assembly of the ETC complex, and OXPHOS; (2) By activating fatty acid oxidation enzymes such as CPT1A and ACADL, it inhibits lipid accumulation and lipotoxicity within cardiomyocytes; (3) Cooperating with HIF-1α to regulate the metabolic switch between glycolysis and OXPHOS, maintaining the energy supply during ischemia/reperfusion injury.

Basic Structure and Function of Nrf-3

Nrf-3 (NFE2L3), as a member of the CNC-bZIP transcriptional activator family, exhibits a relatively low basal expression level. This, to a certain extent, restricts in-depth investigations into its functions.[37] Nevertheless, existing studies have revealed that Nrf-3 may play a crucial role in the regulation of oxidative stress through a non-classical pathway.[38] Unlike Nrf-2, Nrf-3 may not be entirely dependent on the regulatory mechanism mediated by Keap1. Instead, it inhibits the activity of Nrf-2 by competitively binding to the ARE, thereby establishing a negative feedback regulatory mechanism.[39] This mechanism enables cells to more precisely regulate the expression of antioxidant genes when dealing with oxidative stress, and to avoid the potential risks associated with an excessive response (Figure 5).

In terms of the cardiovascular system, the functions of Nrf-3 have gradually attracted attention. Especially in macrophages, Nrf-3 has been proven to be able to inhibit lipid accumulation, and this characteristic is of great significance for delaying the progression of atherosclerosis.[40] Atherosclerosis is a chronic inflammatory disease, and its occurrence and development are closely related to abnormal lipid metabolism, oxidative stress, and inflammatory responses. Nrf-3 reduces lipid accumulation within macrophages by regulating the expression of genes related to lipid metabolism, thus contributing to the alleviation of the inflammatory response and plaque formation in atherosclerosis.

Despite the remarkable cardioprotective potential of Nrf-3, its clinical application still faces challenges. For example, the potential association between Nrf-3 and cancer metabolic reprogramming needs to be carefully evaluated.[41] Current research efforts are focused on developing small-molecule compounds, especially derivatives of boswellic acid, to specifically target Nrf-3 and promote its nuclear translocation. Alternatively, gene editing strategies, such as the use of

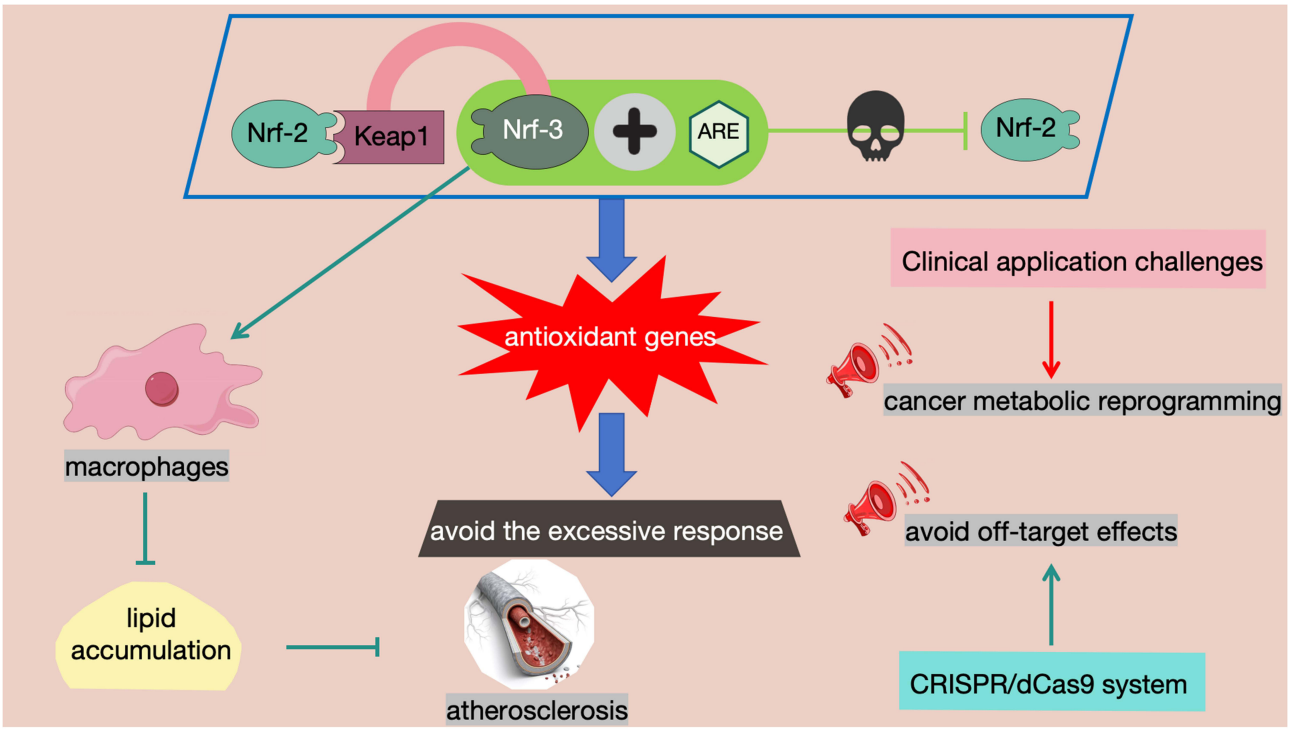

Figure 5 The Negative Feedback Regulation Mechanism by Which Nrf-3 Inhibits the Activity of Nrf-2 through Competitively Binding to the ARE.

the CRISPR/dCas9 system, are being designed to precisely regulate the expression of Nrf-3. The aim is to avoid off-target effects and enhance the specificity and effectiveness of treatment.

Mechanisms of the Nrf Family in Cardiac Health

In the cardiac microenvironment, the Nrf family collaboratively responds to different pathological stimuli through spatiotemporally specific expression patterns. Its mechanisms of action encompass the molecular quenching of oxidative damage, the reprogramming of the inflammatory microenvironment, the dynamic regulation of mitochondrial quality control, and the precise balance of programmed cell death. The following will systematically analyze the four core dimensions of the roles of the Nrf family in cardiac health, including maintaining redox homeostasis, regulating the inflammatory response, improving mitochondrial function, and controlling programmed cell death (apoptosis, autophagy, and pyroptosis).

Maintaining Redox Homeostasis

The heart, as an organ with high oxygen consumption, is vulnerable to oxidative stress. Oxidative stress refers to the imbalance between oxidation and antioxidation in the body, leading to an increased production of ROS. This, in turn, induces the expression of pro-inflammatory genes such as iNOS and TNF-α, causing damage to cardiac cells, which is manifested by an increase in indicators such as serum transferase and CK-MB.[42] The Nrf family plays a crucial role in maintaining redox homeostasis. Among them, Nrf-2 effectively scavenges ROS and free radicals and reduces the damage of oxidative stress to cardiac cells by activating phase II detoxifying enzymes (such as HO-1), promoting the production of antioxidant substances such as SOD, GPx, and CAT, and simultaneously reducing the levels of oxidative substances such as MDA, AOPP, and NO.[43] Studies have shown that Nrf-2 undergoes k48-linked ubiquitination modification in the myocardium of doxorubicin-treated mice through the MALT1 activation pathway dependent on the CaMKII-δ-CARD11-BCL10-MALT1 complex, resulting in a downregulation of its protein level and thus exacerbating myocardial oxidative stress.[44] Subsequent studies have further confirmed that micafungin protects the mouse heart from doxorubicin-induced oxidative damage by inhibiting MALT1-dependent k48-linked ubiquitination of Nrf-2.[45] In addition, research has also

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found that the Nrf-2 signaling pathway mediates the regulation of cardiovascular oxidative stress induced by mild hyperhomocysteinemia through a triple mechanism: (1) Transcriptionally regulating SOD, CAT, and GPx to reconstruct the antioxidant enzyme system; (2) Inhibiting the generation of ROS marked by dichlorofluorescein in the myocardium, and antagonizing the balance between the pro-inflammatory factors IL-1β/IL-6 and the upregulation of the anti-inflammatory factor IL-10; (3) Negatively regulating the activity of serum BuChE through the cholinergic pathway to establish an interactive network of oxidation-inflammation-cholinergic.[46]

Interestingly, by upregulating Nrf-2, the fat-soluble substances in ginger and turmeric can alleviate the oxidative stress in the liver and heart caused by heat and reduce blood pressure.[47] Studies have shown that environmental pollutants such as arsenic trioxide can inhibit the activation of the Nrf-2 pathway, downregulate the expression of antioxidant genes such as Nrf-2, HO-1, and SOD-1, and simultaneously upregulate the expression of Keap1, thereby weakening the antioxidant capacity of the heart.[48] This change leads to cardiac mitochondrial dysfunction, exacerbated oxidative stress, and triggers the apoptosis pathway, manifested by the upregulation of the expression of apoptosis-related genes and proteins such as Caspase 3, Cyt-C, p53, and Bax, as well as the downregulation of the expression of Bcl-2.[49] It is worth noting that research has also found that rutin can effectively prevent the cardiac oxidative stress and inflammatory response caused by exposure to bisphenol A and dibutyl phthalate, and this protective effect is closely related to the regulation of the Nrf-2/NF-κB pathway.[50] In addition, the activation of the Sigma 1 receptor significantly improves right ventricular remodeling and dysfunction in the pulmonary arterial hypertension model by activating the Nrf-2/HO-1 signaling module, further confirming the central regulatory role of Nrf-2 in maintaining myocardial redox homeostasis and resistance to remodeling.[51] Other studies have pointed out that by activating Nrf-2, the total extract of *Abelmoschus manihot (L)*. alleviates radiation-induced ferroptosis in cardiomyocytes by regulating the redox imbalance mediated by the NOX4/xCT/GPX4 axis.[52] These research results further highlight the central role of Nrf-2 in protecting the heart from oxidative stress damage.

Another study has confirmed that Nrf-2 plays a crucial role in the protection of the heart against oxidative stress by royal jelly.[53] Royal jelly activates the Nrf-2/NF-κB and Bcl-2/Bax pathways, reducing oxidative damage to cardiac tissues. Specifically, it is manifested by a decrease in the level of MDA, an increase in the level of GSH, a reduction in the expression of apoptosis-related proteins such as caspase-3, caspase-9, caspase-6, and Gsk-3, and an increase in the expression of BDNF protein. This further highlights the importance of Nrf-2 in resisting oxidative stress and suggests that royal jelly, as a natural product, has the potential to be developed into a drug for treating cardiac oxidative stress damage. In addition, Nrf-2 plays a key role in the anti-oxidative stress and cardiac protection of Yixin-Fumai Granules.[54,55] In the sick sinus syndrome model of naturally aged C57BL/6 slow mice, the activation of Nrf-2 is mediated by Yixin-Fumai Granules. By scavenging ROS, it promotes the expression of itself and the downstream gene HO-1, and then activates SHOX2, promoting the expression of HCN4 in the sinoatrial node of mice. This process depends on the Nrf-2/HO-1 pathway. After the activation of SHOX2, it regulates CACNA1G through the SHOX2/BMP4/GATA4/NKX2-5 axis, improves the function of the T-type calcium channel, effectively inhibits the decline of sinoatrial node function, and accelerates the heart rate. It is worth noting that SGLT2 inhibitors activate the Nrf-2-dependent energy sensing mechanism by mimicking the state of calorie restriction, showing significant potential in regulating cardiovascular and metabolic homeostasis and reducing cardiovascular endpoint events.[56] This finding expands a new direction for the application of Nrf-2-targeted intervention strategies in the prevention and treatment of CVDs.

Regulation of Inflammatory Response

Inflammation plays a pivotal role in the pathogenesis and progression of CVDs. Nrf-2, a member of the Nrf family, has the capacity to suppress the expression of pro-inflammatory genes. It can effectively reduce the production of inflammatory factors such as TNF-α and IL, exerting a remarkable anti-inflammatory effect, and thus safeguarding the heart from inflammatory damage. Mechanistic studies have demonstrated that the overexpression of USP13 leads to a decrease in the level of Nrf-2, which subsequently triggers cell apoptosis, oxidative stress, and the upregulated expression of inflammatory factors.[57] However, the overexpression of the Klotho gene can activate Nrf-2 and the ARE, thereby reducing oxidative stress damage and the inflammatory response following myocardial infarction.[58] Further research has

revealed that the natural alkaloid piperine exerts a significant cardioprotective effect against the inflammatory response associated with myocardial infarction. Its molecular mechanism is mainly related to the coordinated regulation of the Nrf-2/MAPK/NF-κB signaling pathway.[59] This pathway activates the expression of tissue repair-related genes such as HIF-1α and VEGF, and simultaneously regulates the balance between iNOS and eNOS. Consequently, it promotes the biosynthesis of hydroxyproline, enhances the activity of MMP-2/9, and the deposition of type I collagen. Notably, betaine exhibits pharmacological properties similar to those of piperine in terms of combating myocardial inflammatory damage. By inhibiting the iNOS/COX-2 inflammatory axis and activating the Nrf-2/HO-1/Keap1 antioxidant pathway, it can effectively counteract the pathological damage of myocardial inflammation mediated by oxidative stress.[60] In addition, studies have also confirmed that SQSTM1/p62 can alleviate hypoxia-induced cardiac dysfunction by stabilizing HIF-1α and Nrf-2, further highlighting the crucial role of Nrf-2 in cardioprotection.[61]

The activation of Nrf-2 plays a crucial role in the protection against doxorubicin- and avermectin-induced cardiotoxicity by hemin and palliative.[62,63] Specifically, the activation of the Nrf-2/HO-1 and Nrf-2/Keap1 signaling pathways, along with their positive and negative regulatory mechanisms, provides effective protection for the heart against the toxic effects of doxorubicin and avermectin. Under the action of doxorubicin and avermectin, the heart shows toxic manifestations, including a significant increase in myocardial enzymes and the level of MDA, and an upward trend in the level of Keap1. Meanwhile, the gene expression of antioxidant genes such as GSR, HO-1, GPX, SOD, and CAT decreases. In addition, inflammatory and apoptotic-related indicators such as TLR-5, cleaved caspase-3, JAK1, STAT3, NF-κB, TNF-α, CRP, IP-10, IL-1β, MCP-1, IL-6, and COX-2 also show an upward trend, accompanied by toxic histopathological changes. The combined use of hemin and doxorubicin significantly enhances the antioxidant capacity of the heart by activating the Nrf-2/HO-1 pathway, and effectively inhibits the activation of the TLR-5/NF-κB/TNF-α inflammatory pathway, thereby reducing doxorubicin-induced cardiotoxicity in a dose-dependent manner. On the other hand, palliative significantly protects cardiac tissues by regulating relevant indicators. Its mechanism is also closely related to the positive feedback regulation of Nrf-2/Keap1, and it simultaneously regulates the JAK1/STAT3 and NF-κB pathways.

In addition, the anti-inflammatory effect of Nrf-2 is not limited to the above. Under the action of kolaviron, Nrf-2 exerts its anti-inflammatory regulatory function in the hearts of type 2 diabetes mellitus patients.[64] The upregulation of Nrf-2 expression activates the downstream antioxidant gene SOD-2 and the pro-survival pathway AKT-1/eNOS, effectively enhancing the antioxidant capacity of the heart and improving vascular function. At the same time, the activation of Nrf-2 also inhibits the pro-inflammatory/pro-apoptotic pathways, including NF-κB, PKC-α, ACE, p38 MAPK, etc., significantly reducing the levels of inflammatory factors and the oxidative stress response. In addition, Nrf-2 also precisely regulates glucose and lipid metabolism and cell survival by balancing the mTOR/P70S60K signaling pathway. It is worth noting that Nrf-2/HO-1 also plays an important role in rescuing myocardial necrosis under the action of erdostein, and further exerts its anti-inflammatory effect by blocking the MAPK pathway.[65] Marsin-1 (a pro-resolving lipid mediator) inhibits lipopolysaccharide-induced M1 polarization of macrophages (reducing the secretion of pro-inflammatory factors) and promotes M2 polarization (enhancing the expression of anti-inflammatory mediators) by targeting and regulating the phenotypic polarization of macrophages. At the same time, it synergistically activates the Nrf-2/HO-1 antioxidant pathway, effectively inhibits the oxidative stress-inflammation cascade reaction, and ultimately achieves the cardioprotective effect.[66] Its mechanism reveals the synergistic effect of Nrf-2-mediated macrophage immune reprogramming and the regulation of redox homeostasis. These mechanisms work together to effectively protect the heart from inflammatory and oxidative stress damage.

Improvement of Mitochondrial Function

Members of the Nrf family maintain the homeostasis of mitochondrial function through specific regulatory mechanisms: the oxidative stress defense network mediated by Nrf-2, the mitochondrial biogenesis and metabolic reprogramming regulated by Nrf-1, and the biphasic regulatory function of Nrf-3 in pathological mitochondrial damage.

Mitochondrial Protection Network Mediated by Nrf-2

Nrf-2 directly interacts with the mitochondrial membrane protein PGAM5 to regulate the activation state of the mitochondrial unfolded protein response, significantly improving mitochondrial respiratory function and thus enhancing the energy metabolism ability of cardiomyocytes under stress conditions.[67] Under oxidative stress conditions, Nrf-2 effectively alleviates the redox imbalance caused by the excessive accumulation of ROS by coordinating the antioxidant defense system and the mitochondrial quality control network. An acid-responsive supramolecular peptide conjugate (ISP) developed based on this mechanism - constructed by the Nrf-2 activator OI and the mitochondria-targeting peptide SS31 through a cleavable linker - can self-assemble into nanofibers in the acidic microenvironment of myocardial ischemia/reperfusion injury and exert a therapeutic effect through a dual synergistic mechanism: the OI component promotes the release and activation of Nrf-2 by binding to Keap1 with high affinity, while the SS31 peptide directionally repairs mitochondrial function, jointly restoring redox homeostasis and reducing myocardial damage.[68]

The latest research shows that Nrf-2 plays a central role in maintaining mitochondrial function homeostasis through a multi-dimensional regulatory mechanism. At the molecular regulation level, after Nrf-2 is activated by nuclear translocation through the ubiquitination and degradation pathway of Keap1 mediated by USP7, it effectively curbs mitochondrial iron overload and the process of lipid peroxidation by reconstructing the iron metabolism network (downregulating GPX4, upregulating PTGS2 and ACSL4), and significantly reduces the pathological damage of myocardial infarction induced by ferroptosis.[69] Further research has found that the activation of the AMPK/Nrf-2/HO-1 signaling axis can significantly enhance the activities of antioxidant enzyme systems such as GPX, CAT, and SOD, thereby specifically antagonizing the mitochondrial oxidative damage and the apoptosis cascade reaction triggered by environmental toxins such as 1-nitropyrene.[70] Mechanistic studies have confirmed that butyrate and resolvin D1 can not only repair the dysfunction of the mitochondrial electron transport chain in cardiomyocytes caused by oxidative stress by targeting and activating the Nrf-2 signaling pathway, but also alleviate the unfolded protein response through coordinating the endoplasmic reticulum-mitochondria coupling mechanism, providing a new molecular intervention strategy for myocardial protection.[71,72] It is noteworthy that fecal microbiota transplantation regulates the Nrf-2-dependent mitochondrial dynamic balance (including the phosphorylation modification of mitochondrial fission factor DRP1and the subcellular localization of the fusion protein OPA1) through the gut-heart axis, which significantly reduces the sensitivity to myocardial toxic damage while improving the structural integrity of mitochondrial cristae.[73]

Nrf-2, through phosphorylation activation mediated by electroacupuncture preconditioning, synergizes with the AMPK signaling pathway to inhibit DRP1-dependent excessive mitochondrial fission, significantly improving mitochondrial morphology and function, and thus reducing myocardial ischemia-reperfusion injury.[74] Notably, the natural active ingredient icariin further expands the biological functions of Nrf-2. By targeting and activating the SIRT1-Nrf-2-HO-1 axis, it downregulates the expression of ACSL4, a key driver of ferroptosis, and p53, while upregulating the expression of GPX4 and FTH1. It reshapes the homeostasis of mitochondrial iron metabolism and blocks the peroxidation process of PUFA, ultimately reversing the pathological phenotypes of mitochondrial cristae structure disintegration, respiratory chain dysfunction, and atrial electrical remodeling induced by ethanol, highlighting the central role of the Nrf-2 signaling network in antagonizing ferroptosis and maintaining myocardial homeostasis.[75] Echoing this mechanism, the farnesoid X receptor agonist obeticholic acid exerts a cardioprotective effect by activating the Nrf-2-mediated mitochondrial quality control system. It inhibits the excessive activation of the ERK1/2-DRP1 signaling axis, preventing pathological mitochondrial fission. Meanwhile, it upregulates the expression of subunits of respiratory chain complex I and reduces the leakage of Cyt-C from mitochondria, ultimately improving the efficiency of mitochondrial oxidative phosphorylation and the homeostasis of energy metabolism.[76] These three studies jointly reveal the multi-dimensional regulatory value of Nrf-2 in coordinating the structural and functional integrity of mitochondria.

Nrf-1-Driven Mitochondrial Biogenesis and Metabolic Regulation

Verbascoside promotes mitochondrial biogenesis by activating Nrf-1, thus alleviating the cardiotoxicity induced by triptolide. In addition, the crosstalk between the Nrf-2/Nrf-1 signals can enhance the detoxification effect of calycosin and further promote mitochondrial biosynthesis.[77] This process involves the regulation of the Nrf-2-Keap1-PGC1α axis and is closely related to the depolymerization of F-actin and the increase in ATP production. The latest research reveals

that the cardioprotective mechanism of empagliflozin has multi-dimensional regulatory characteristics: it not only establishes a systemic antioxidant defense barrier by activating Nrf-2 but also significantly enhances mitochondrial biogenesis and the efficiency of the respiratory chain through the PGC-1α/Nrf-1 signaling axis. This dual effect effectively improves the stability of myocardial electrical activity by optimizing the efficiency of mitochondrial oxidative phosphorylation, thereby suppressing the occurrence of arrhythmia.[78]

In-depth studies have shown that Nrf-1 has a core function independent of Nrf-2 in regulating mitochondrial homeostasis. Under intermittent cold exposure conditions, Nrf-1 is upregulated, significantly enhancing the antioxidant defense and metabolic capabilities of mitochondria. This is specifically manifested by the enhanced activities and expressions of manganese SOD and SDH in cardiac tissues.[79] Meanwhile, Nrf-1 also promotes mitochondrial biogenesis, resulting in a significant increase in the copy number of mitochondrial DNA, and upregulates the expressions of its upstream regulator PGC-1α and TFAM. Intermittent cold exposure also increases the level of sirtuin 3 in cardiac mitochondria and reduces the degree of total protein lysine acetylation, suggesting an enhanced activity of sirtuin, which is closely related to the regulatory effect of Nrf-1. PKA plays a central role in regulating mitochondrial biogenesis and function, which is further demonstrated by its effective inhibition of the production of PGC-1α and Nrf-1, especially highlighting the key position of Nrf-1 in expression regulation.

The Role of Nrf-3 in Pathological Mitochondrial Damage

The latest research shows that Nrf-3 inhibits Pitx2 by regulating the level of mitochondrial superoxide, thereby promoting cardiomyocyte apoptosis and leading to cardiac dysfunction.[80] Studies have confirmed that as a key molecule regulating mitochondrial ROS, Nrf-3 significantly increases the production of mitochondrial ROS and the apoptosis rate of cardiomyocytes by inhibiting the transcriptional expression of Pitx2 after myocardial infarction. This not only increases the mortality rate in the acute phase but also exacerbates the process of ventricular remodeling.

Analysis of clinical samples has revealed a significant upregulation of Nrf-3 expression in the lesioned areas of patients with myocardial infarction. A collaborative study between Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine and Queen Mary University of London further validated these findings through the analysis of single-cell transcriptomic data from human hearts and tissue samples of myocardial infarction patients. Moreover, animal experiments demonstrated that Nrf-3 gene knockout could reduce the acute-phase mortality of myocardial infarction, ameliorate ventricular remodeling, and improve cardiac function. In addition, overexpression of Nrf-3 exacerbated mitochondrial ROS accumulation and apoptotic processes in human induced pluripotent stem cell-derived cardiomyocytes following hydrogen peroxide stimulation.

This study elucidates the core pathophysiological mechanism of myocardial injury and protection, suggesting that targeted intervention in the Nrf-3/Pitx2 signaling axis may become a potential therapeutic strategy for improving the myocardial survival rate, cardiac function, and prognosis of patients with acute myocardial infarction, which has clear clinical transformation significance.

Regulation of Apoptosis, Autophagy and Pyroptosis

The Nrf family significantly reduces myocardial cell damage by precisely regulating the dynamic balance of three programmed cell death pathways: apoptosis, autophagy, and pyroptosis.

Regulation of Cell Apoptosis

Nrf-2 plays a multi-dimensional cardioprotective role in the progression of coronary heart disease (Figure 6). Mechanistic studies have shown that Nrf-2 achieves a synergistic regulatory effect by integrating the dual signaling pathways of GAS5/miR-495-3p/SIX1 and IGF2BP2: it optimizes the energy metabolism of cardiomyocytes by promoting glycolytic reprogramming, and at the same time enhances the ferroptosis resistance of endothelial progenitor cells through the GPX4-mediated antioxidant defense system, thus significantly inhibiting the apoptosis process of cardiomyocytes.[81] Further studies have found that the Nrf family finely regulates cell apoptosis through the following mechanisms: 1) Transcriptionally activates the expression of anti-apoptotic genes; 2) Maintains the integrity of the myocardial structural protein network (connexin 43, α-actin, and myosin light chain); 3) Stabilizes the cell membrane

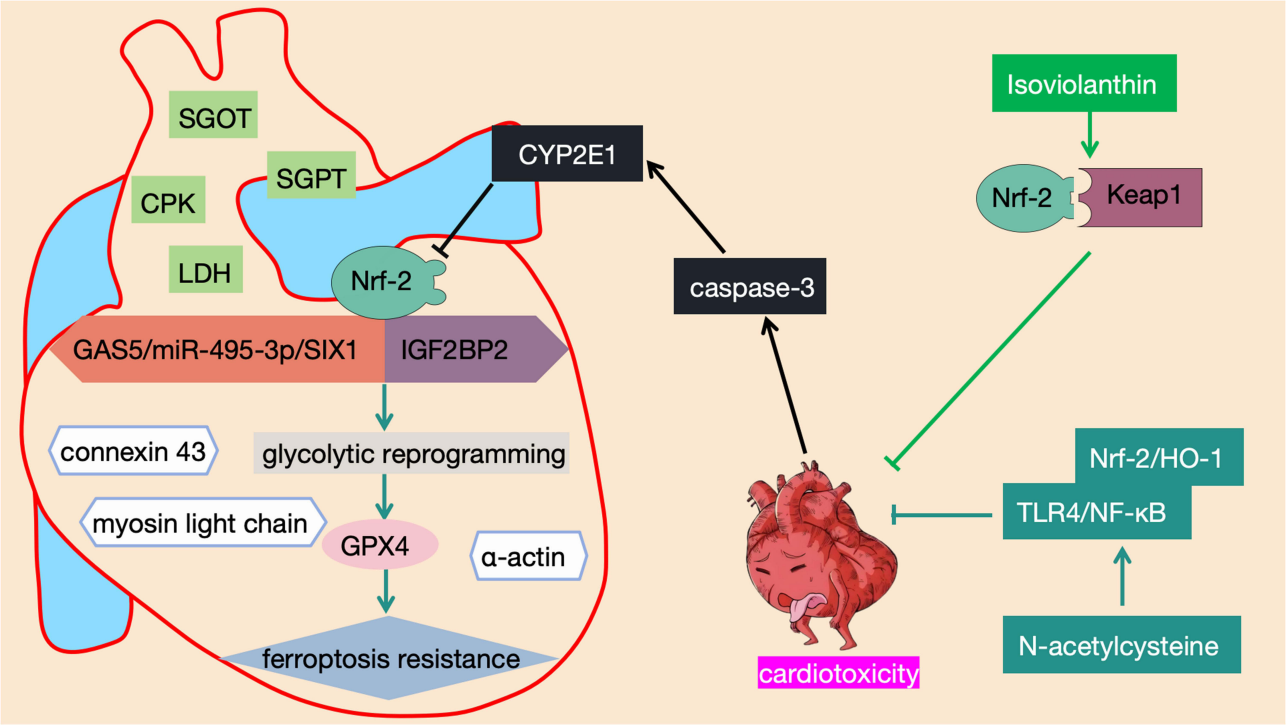

Figure 6 The Molecular Network and Protective Mechanism of the Nrf Family in Regulating Myocardial Cell Apoptosis.

structure and reduces the release of myocardial injury markers (SGOT, SGPT, CPK, LDH). The latest treatment strategy has confirmed that the Nrf-2 targeted delivery system based on alginate-gelatin microspheres can effectively regulate the above-mentioned apoptosis-related pathways, verifying its central position in cardioprotection.[82]

Further studies have also confirmed that Nrf-2 plays a key role in inhibiting drug-induced cardiotoxicity. The CYP2E1-mediated inhibition of Nrf-2 expression is the core cause of mitoxantrone-induced cardiotoxicity. The loss of its function leads to the activation of caspase-3 and the abnormal elevation of myocardial injury markers. Targeted inhibition of CYP2E1 can alleviate the related toxicity by activating the Nrf-2 pathway.[83] It is worth noting that recent studies have found that isoviolanthin can precisely regulate the Nrf-2/Keap-1 antioxidant signaling axis, simultaneously inhibit the inflammatory cascade reaction and programmed apoptotic death, and significantly improve the histopathological characteristics of the myocardial tissue, thereby achieving the goal of inhibiting cardiotoxicity.[84] In addition, N-acetylcysteine inhibits the expression of apoptosis-related factors and alleviates 5-fluorouracil-induced cardiotoxicity by dual regulation of the TLR4/NF-κB and Nrf-2/HO-1 signaling pathways.[85]

Regulation of Cellular Autophagy

As a highly regulated programmed cell death mechanism, cellular autophagy plays a crucial role in the occurrence and development of CVDs[86] (Figure 7). Among them, Nrf-2 precisely regulates the autophagy process through a dual mechanism: on the one hand, it maintains the autophagic flux by regulating the expression levels of the LC3B-II/LC3B-I ratio (a marker of autophagosome formation) and SQSTM1/p62 (an autophagic substrate adaptor protein); on the other hand, it continuously activates the antioxidant response through the p62-Keap1-Nrf-2 positive feedback loop. This regulatory network can effectively remove damaged organelles and abnormal protein aggregates, which is essential for maintaining the homeostasis of cardiomyocytes.[87] It is particularly noteworthy that the cardioprotective peptide NPA7 significantly enhances autophagic activity via the p62-KEAP1-Nrf-2 pathway through dual targeting of the GC-A/cGMP and MasR/cAMP signaling systems, while reducing the generation of ROS mediated by NOX2.[88] The latest mechanistic studies further confirm that the specific activation of Nrf-2 combined with Mst1 gene knockout can significantly enhance the autophagic activity of cardiomyocytes. This intervention strategy can not only improve cardiac systolic function,

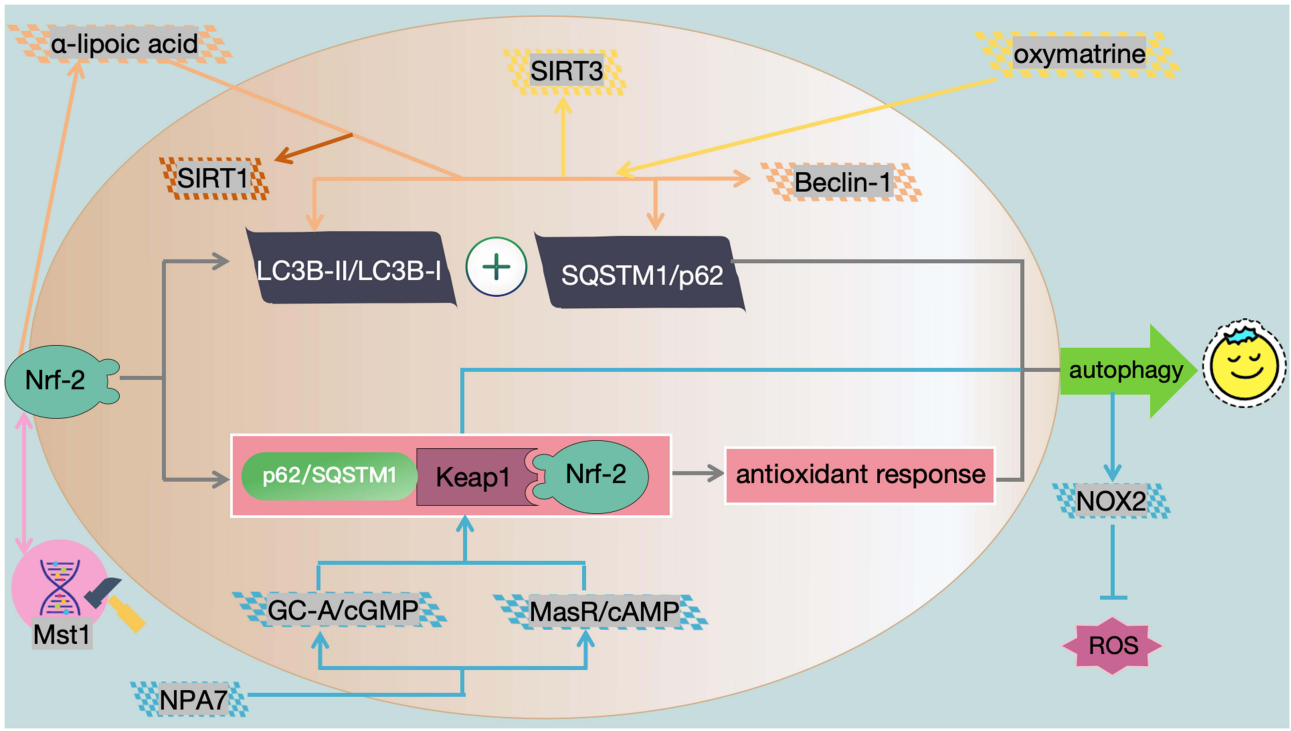

Figure 7 The Mechanism of Action of the Nrf Family in Regulating Myocardial Homeostasis through Autophagy.

reduce myocardial fibrosis, but also inhibit cardiomyocyte apoptosis, providing a new molecular intervention target for the targeted treatment of diabetic cardiomyopathy.[89]

In the myocardial injury induced by intermittent hypoxia, Nrf-2 activates the autophagy signaling pathway by mediating the antioxidant effect of α-lipoic acid, which is manifested as a significant increase in the LC3-II/LC3-I ratio, upregulation of Beclin-1 expression, and enhanced degradation of SQSTM1/p62. Consequently, it improves the ability of cardiomyocytes to clear misfolded or aggregated proteins and damaged or aged organelles. Ultimately, it plays a crucial cardioprotective role by maintaining cellular homeostasis and reducing oxidative stress damage.[90] In the myocardial infarction model, Nrf-2 is activated through nuclear translocation mediated by α-lipoic acid. It synergistically stabilizes the expression of SIRT1 protein, significantly inhibits the generation of ROS, and regulates the autophagic flux, effectively alleviating age-dependent macrophage senescence and ultimately improving myocardial injury.[91] In the aldosterone-induced myocardial hypertrophy model, Nrf-2 mediates the cardioprotective effect of oxymatrine. It significantly upregulates the transcriptional activity of SIRT3, thereby restoring the autophagic flux (characterized by an increase in the LC3-II/LC3-I ratio and p62 degradation), maintaining the mitochondrial membrane potential and morphological integrity. Finally, it effectively inhibits the process of pathological myocardial hypertrophy.[92]

Regulation of Pyroptosis

The activation of Nrf-2 regulates the pyroptosis of cardiomyocytes through multiple mechanisms, including the control of PPAR-γ/HO-1, NF-κB/IL-6/Keap-1, and Bcl-2/caspase-3/ATG-5. Its core functions are as follows: specifically inhibiting the activation of the NLRP3 inflammasome and significantly reducing the expression of key pyroptosis effector proteins (ASC, caspase-1, and GSDMD). At the same time, by improving mitochondrial function, reducing the levels of oxidative stress markers (MDA) and pro-inflammatory factors (IL-1β, IL-18), it synergistically alleviates myocardial injury (Figure 8). In relevant studies, intervention measures (such as oxyresveratrol and/or dapagliflozin) can significantly improve histopathological damage by activating Nrf-2, achieving effective regulation of cardiomyocyte pyroptosis.[93] In the doxorubicin model, the signal transduction of Nrf-2 is regulated by the RIP3-AKT cascade, and the blockade of its signal directly exacerbates the processes of oxidative stress and myocardial pyroptosis.[94]

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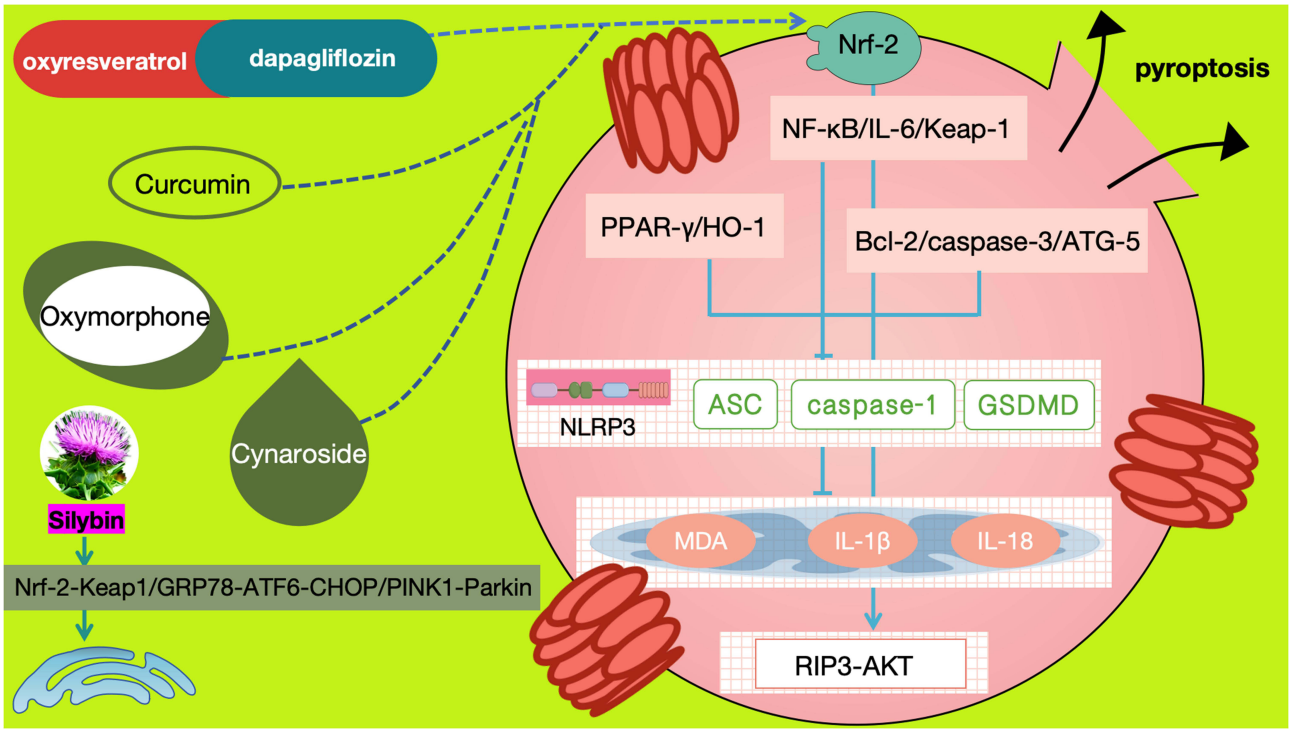

Figure 8 The Regulatory Pathways and Functions of the Nrf Family in Mediating Myocardial Cell Pyroptosis.

Studies have shown that Nrf-2 regulates the mechanism through the Akt/ARE pathway activated by curcumin, specifically transcriptionally activating HO-1 and GCLC, thereby antagonizing the abnormal accumulation of ROS and mitochondrial ultrastructural damage in diabetic cardiomyopathy. This regulatory network effectively inhibits the process of high glucose-induced pyroptosis by blocking the NLRP3 inflammasome/Caspase-1 signaling axis, providing a new target for molecular intervention in diabetic cardiomyopathy.[95] In addition, cynaroside inhibits doxorubicin-induced pyroptosis of cardiomyocytes by regulating the AMPK/SIRT3/Nrf-2 pathway.[96] Oxymorphone, on the other hand, inhibits inflammation, oxidation, and pyroptosis through the Nrf-2/HO-1 signaling pathway, alleviating lipopolysaccharide-induced myocardial injury.[97] Silybin specifically activates the Nrf-2-Keap1/GRP78-ATF6-CHOP/PINK1-Parkin signaling pathway, reducing cardiac endoplasmic reticulum stress, blocking apoptosis, and inhibiting the initiation of excessive autophagy, thus antagonizing the cardiotoxicity induced by avermectin.[98] These research achievements systematically reveal the positive role of Nrf-2 in regulating pyroptosis and its central position in maintaining the homeostasis of cardiomyocytes.

The Role of the Nrf Family in CVDs

Members of the Nrf family play a crucial role in the pathological processes of various CVDs by regulating the redox balance, inflammatory response, and metabolic homeostasis. The changes in their activities are closely related to the occurrence, development, and prognosis of the diseases, making them potential therapeutic targets. The following will systematically elaborate on the specific mechanisms of action and therapeutic potential of the Nrf family in different CVDs.

Myocardial Ischemia-Reperfusion Injury

The Nrf family plays a central regulatory role in the pathological process of myocardial ischemia-reperfusion injury. Studies have shown that bombesin, a non-adrenergic and non-cholinergic neuropeptide derived from the vagus nerve of the gastric antrum mucosa, can reduce myocardial ischemia/reperfusion injury by activating the Nrf-2-Keap1-HO-1 signaling pathway.[99] In addition, bardoxolone methyl has the effect of improving myocardial ischemia/reperfusion injury

by activating the Nrf-2/HO-1 signaling pathway.[100] Similarly, the protective mechanism of parecoxib sodium in the rat model of myocardial ischemia-reperfusion injury also depends on the activation of the Nrf-2 signaling axis. Specifically, parecoxib sodium selectively upregulates the expression of phase II detoxifying enzymes such as HO-1 and GST by regulating the Nrf-2/NF-κB signaling cascade. At the same time, it regulates the ratio of Bcl-2/Bax proteins, thereby reducing the levels of ROS and the accumulation of lipid peroxidation products in myocardial tissue from multiple dimensions. The above regulatory network significantly inhibits the expression of pro-inflammatory factors (TNF-α, IL-6) and inflammatory mediators (COX-2, iNOS). Finally, it achieves the dual inhibition of redox homeostasis reconstruction and the inflammatory cascade reaction, providing an experimental basis for the Nrf-2 targeted therapeutic strategy.[101] Interestingly, Nrf-2/HO-1 plays a key role in the mechanism of action of DJ-1 (also known as PARK7, a Parkinson's disease-related deglycase). Its activation may be one of the main downstream mechanisms by which DJ-1 retains the cardioprotective effect of post-ischemic adaptation against myocardial ischemia/ischemic injury in diabetic rats through nuclear and mitochondrial translocation. This process also involves the inhibition of cardiac PTEN.[102]

As a core regulatory factor of the oxidative stress defense system, Nrf-2 exerts a cardioprotective effect through multi-dimensional mechanisms. Studies have shown that in myocardial ischemia-reperfusion injury, Nrf-2 achieves a protective effect through the following synergistic pathways: (1) It mediates the activation of the HO-1 signaling pathway by Apelin-13, significantly enhancing mitochondrial function (manifested as improved membrane potential stability and ATP generation capacity) and inhibiting ferroptosis (by reducing Fe^{2+} accumulation and FTH1 expression);[103] (2) It interacts with SUZ12 to form a positive feedback regulatory loop, continuously upregulating its own expression, and bidirectionally regulating the homeostasis of iron metabolism and the process of ferroptosis;[104] (3) It relieves the inhibition of the xCT/GPX4/HO-1 signaling axis by HDAC1, while reducing apoptosis and the inflammatory response.[105] It is worth noting that this regulatory network has universality across models: In the isoproterenol-induced model, 6-Shogaol significantly reduces the levels of oxidative stress markers (TBARS, LOOH) and pro-inflammatory factors (IL-6, TNF-α) by activating the Nrf-2/HO-1 axis, and simultaneously inhibits the Fas-mediated apoptotic pathway. These findings systematically elucidate the central pivotal role of the Nrf-2 pathway in integrating redox balance, inflammatory regulation, and the inhibition of cell death.[106]

As a core regulatory factor, Nrf-2 plays a crucial protective role in the pathological process of myocardial ischemia-reperfusion injury exacerbated by diabetes.[107] The downregulation of its function directly leads to the inactivation of the BAG3/Bcl-2/HO-1 synergistic protective network, exacerbates the oxidative stress mediated by NADPH oxidase (p22/p67) and the caspase-3/PARP-dependent apoptotic cascade reaction. At the same time, it weakens the myocardial antioxidant defense ability and ultimately amplifies the left ventricular dysfunction induced by ischemia-reperfusion. Targeted restoration of Nrf-2 signaling activity can antagonize the microvascular reactivity injury of the diabetic heart, providing a key molecular target for improving the tolerance of myocardial ischemia-reperfusion injury under the state of metabolic disorder. In addition to Nrf-2, studies have confirmed that Nrf-1 also plays a key role in diabetic myocardial ischemia-reperfusion injury, and its expression is regulated by hypoadiponectinemia.[108] Hypoadiponectinemia upregulates miR-449b, which in turn inhibits the expression of Nrf-1 and the downstream Ucp3. This inhibitory effect leads to exacerbated oxidative stress, increased superoxide production, increased apoptosis, enhanced caspase-3 activity, and at the same time, an enlarged myocardial infarction area and impaired left ventricular function. Antagonizing miR-449b or supplementing exogenous APN can restore the activity of the Nrf-1/Ucp3 pathway, reduce oxidative stress, decrease apoptosis, improve cardiac function, and reduce the infarct size. The APN/miR-449b/Nrf-1 axis is a key target for diabetic myocardial ischemia-reperfusion injury, providing new ideas for treatment.

Atherosclerosis

The formation of atherosclerosis is the pathological basis for the onset of ischemic CVDs. Its pathogenesis is complex and intricate, involving multiple aspects regulated by the Nrf-2/ARE signaling pathway, including inflammatory response, oxidative stress state, apoptosis process, vascular endothelial cell injury, foam cell formation, platelet activation, and other multiple factors.[109,110] Nrf-2, by regulating the SLC7A11/GPX4 pathway, collaborates with berberine to inhibit iron deposition and stabilize atherosclerotic plaques, thus exerting a protective effect on the cardiovascular system.[111] Nrf-2, through the activation of endothelial cells mediated by lycopene, significantly inhibits the formation of

atherosclerotic plaques and reduces the intima-media thickness of the aorta.[112] CO, an enzymatic by-product of HO-1, plays a key role in atherosclerosis and has anti-inflammatory properties.[113] Studies have confirmed that CO drives the polarization of macrophages towards the M2 phenotype by activating the Nrf-2/HO-1 signaling axis, inducing a spindle-shaped morphological transformation and upregulating the expression of surface markers F4/80 and CD11b. At the same time, it promotes the expression of M2-specific molecules (Ym1, Fizz1, arginase-1, IL-10) through the activation of the STAT6/PPARγ pathway and significantly inhibits the production of the pro-inflammatory mediator iNOS. This regulatory mechanism remodels the inflammatory microenvironment of atherosclerotic plaques by enhancing the anti-inflammatory activity, efferocytosis function, and tissue repair ability of M2 macrophages, thereby inhibiting plaque progression. Targeted intervention of the Nrf-2-HO-1/CO-M2 polarization axis provides an important theoretical basis for regulating the immune phenotype of macrophages and developing novel anti-atherosclerotic treatment strategies.

Vascular endothelial dysfunction is one of the etiological factors of atherosclerosis. The functional defect of Nrf-2, as a core molecular mechanism of atherosclerosis, accelerates the disease process through an integrated pathological network. Its downregulated expression induces a cascade effect of oxidative stress-inflammatory response-endothelial dysfunction. At the same time, it leads to dyslipidemia, vascular remodeling (collagen deposition), and overexpression of VCAM-1, synergistically promoting cell cycle arrest and apoptosis, and ultimately forming a pathological cycle that drives the progression of atherosclerosis.[114] However, Nrf-2 plays a "dual role" in 3-BrFlu-induced endothelial dysfunction: on the one hand, it initiates the antioxidant defense to alleviate ROS damage, and on the other hand, its compensatory ability is limited by the overwhelming activation of the inflammatory pathway and the insufficiency of its own efficacy.[115] The specific mechanisms may involve the following: Nrf-2 usually exerts a protective effect by inhibiting the NF-κB inflammatory pathway. However, the excessive activation of the MAPK/NF-κB signaling induced by 3-BrFlu may inhibit the antioxidant efficacy of Nrf-2, forming an "oxidative-inflammatory vicious cycle". As a downstream effector molecule of Nrf-2, the upregulated expression of HO-1 may alleviate inflammation by generating anti-inflammatory products (such as CO), but it fails to effectively antagonize the pro-inflammatory effects of COX2/PGE2, suggesting that the function of HO-1 is counteracted by other mechanisms. In contrast, *Carthamus tinctorius L*. can significantly inhibit the vascular inflammation of human umbilical vein endothelial cells by specifically activating the Nrf-2/HO-1 signaling axis, further confirming the central role of the Nrf-2 pathway in the regulation of vascular homeostasis.[116] Similarly, geraniol from lemongrass can effectively inhibit the release of inflammatory factors from endothelial cells and the adhesion of monocytes induced by Ox-LDL through the synergistic regulation of the Nrf-2/HO-1 and PI3K/Akt signaling pathways, highlighting the broad applicability of the Nrf-2 pathway as a target for pharmacological intervention.[117]

In addition, recent studies have shown that the regulation of oxidative stress related to the Nrf family also plays a crucial role in vascular calcification.[118] Sirt7 (an NAD+-dependent histone deacetylase) inhibits the accumulation of ROS in vascular smooth muscle cells and the Nrf-2-mediated oxidative stress response through its deacetylase activity, delays cell cycle arrest (an increase in the proportion of the G1 phase) and the expression of senescence markers (p16, p21), and thus reduces the deposition of calcium salts. The knockdown of Sirt7 can significantly increase the ROS level and the calcification process, while the ROS inhibitor NAC can reverse this effect. This finding suggests that the Sirt7-ROS-Nrf-2 axis, by regulating the oxidative damage and senescence of VSMCs, becomes a potential target for intervening in vascular calcification. It is worth noting that vascular calcification is not only a key pathological link in the formation of the inflammatory microenvironment of atherosclerotic plaques, but also its mechanism of occurrence shows tissue-specific differences. For example, in the pathological context of diabetes, the S100A9-RAGE axis drives the formation of microcalcifications in extracellular vesicles by activating the pre-calcified phenotype of macrophages. This process is closely related to the dynamic imbalance between the inhibition of the Nrf-2 antioxidant pathway and the abnormal activation of the NF-κB pro-inflammatory signal, suggesting that the disorder of the oxidative-inflammatory homeostasis of macrophages is an important driving force for the formation of the pre-calcified microenvironment.[119]

Heart Failure

Heart failure is a complex cardiovascular syndrome, and its pathogenesis involves multiple factors, including hypoxia-induced myocardial cell apoptosis. Recent studies have revealed that Nrf-2, mediated by AKR1C3, plays a crucial role in

protecting myocardial cells from hypoxic damage.[120] In a hypoxic microenvironment, myocardial cell apoptosis is exacerbated. Overexpression of AKR1C3 promotes the proliferation and viability of myocardial cells, while silencing has the opposite effect. The core of its mechanism lies in the regulation of Nrf-2: On one hand, Nrf-2 reduces the level of ROS, protects mitochondria, maintains the oxygen consumption rate and ATP production, thus effectively defending against hypoxia-induced myocardial cell apoptosis. On the other hand, Nrf-2 is upregulated through the ubiquitin-proteasome pathway in myocardial cells, inhibits the NF-κB signaling, blocks the Bax/caspase-3 pathway, and reduces myocardial cell apoptosis. By regulating the AKR1C3/NF-κB axis, Nrf-2 plays a key role in preventing hypoxic myocardial damage, providing a new perspective for myocardial protection in CVDs such as heart failure. Studies have further confirmed that icariin improves the oxidative stress-related inflammatory response, cell apoptosis, and heart failure phenotype induced by isoproterenol in Wistar rats by regulating the Nrf-2/NF-κB signaling axis. This provides a theoretical basis for the development of novel myocardial protection strategies based on the Nrf-2/AKR1C3 molecular axis.[121] In addition, dapagliflozin inhibits ferroptosis and improves chronic heart failure by regulating the Nrf-2/HO-1/GPX4 signaling pathway.[122]

Cardiac-specific overexpression of ADCY8, through activating the Nrf-2 pathway and its downstream antioxidant and metabolic regulation network, synergistically scavenges ROS, enhances proteasome activity and autophagy, maintains redox homeostasis, and inhibits apoptosis, thus establishing a systematic cardiac protection mechanism. The activation of Nrf-2 drives metabolic reprogramming, including the shift from fatty acid oxidation to aerobic glycolysis, an increase in the flux of the pentose phosphate pathway, and enhanced nucleotide synthesis. It stabilizes the levels of ATP and phosphocreatine, supporting the energy metabolism demands of the heart under long-term high load (with an increase of 30% in heart rate, ejection fraction, and cardiac output). Structurally, the overexpression of ADCY8 induces a reduction in the volume of the left ventricular cavity, compensatory thickening of the ventricular wall, and miniaturization of myocardial cell volume. Collaborating with the functional remodeling mediated by Nrf-2, it avoids the markers of pathological myocardial hypertrophy and achieves long-term stability of cardiac function without phenotypes of heart failure or death. Complementary to the mechanism of AKR1C3 in promoting myocardial proliferation, the ADCY8/Nrf-2 axis, through the synergistic regulation of antioxidant defense and metabolic flexibility, provides a new target for the treatment of heart failure, suggesting that targeting Nrf-2 and its pathway can promote the functional repair of pathological cardiac injury.[123]

DOX, as a broad-spectrum anthracycline chemotherapy drug, although it has significant efficacy in the treatment of solid tumors, its dose-limiting cardiotoxicity (such as cardiomyopathy and heart failure) severely restricts its clinical application. Studies have shown that berberine, by targeting and activating the Nrf-2 signaling pathway, can coordinately regulate the dual mechanisms of oxidative stress scavenging and fibrosis inhibition, thereby antagonizing DOX-induced cardiac injury.[124] Specifically, berberine promotes the nuclear translocation of Nrf-2, upregulates the expression of downstream antioxidant effector molecules HO-1 and mitochondrial function regulator TFAM, effectively scavenges ROS, repairs the mitochondrial membrane potential, and inhibits myocardial cell apoptosis. At the same time, its significant downregulation of pro-fibrotic markers α-SMA and type I/III collagen further improves the pathological remodeling of myocardial tissue fibrosis, ultimately achieving dual protection of myocardial structure and function. Recent studies have further revealed that SIRT6 can improve mitochondrial kinetic disorders and restore mitochondrial membrane integrity and ATP synthesis ability by activating the Nrf-2/FUNDC1 signaling axis (FUN14 domain-containing protein 1, a key regulator of mitophagy), thus alleviating the pathological process of DOX-induced cardiomyopathy.[125] In addition, cevanine, a quinazoline carbalkali alkaloid derived from the medicinal plant Cornus officinalis, promotes the expression of GCLM by activating the Nrf-2-HO-1/AKT signaling cascade, showing a significant alleviating effect on DOX cardiotoxicity, further expanding the pharmacological value of the Nrf-2 signaling network in myocardial protection.[126] Troxerutin, on the other hand, effectively antagonizes DOX-induced cardiac injury by inducing antioxidant properties, restoring mitochondrial function, and upregulating the expression of the myocardial Nrf-2/SIRT-1/PGC-1α network.[127]

Other CVDs

The Nrf family also plays an important role in other CVDs. In the model of diabetic cardiomyopathy, Nrf-2, through the dual inhibition mechanism of the MAPK/NF-κB signaling axis mediated by bicyclol, significantly improves insulin resistance and alleviates myocardial lipotoxicity. Its core target sites involve key regulatory nodes of the inflammatory response and oxidative stress.[128] Further studies have also confirmed that the targeted activation of the Nrf-2 signaling pathway can mediate the myocardial protective effect of Tongmai Jiangtang Capsule: by upregulating the expression of NQO1, HO-1, and SOD2, it remodels the redox homeostasis. At the same time, it inhibits the deposition of the myofibroblast transdifferentiation marker α-SMA and the extracellular matrix componentCol-1, thus coordinately intervening in the process of diabetic myocardial fibrosis.[129] Endoplasmic reticulum stress, as the core hub of the oxidative stress-inflammatory cascade, can accelerate the progression of CVDs by inducing endothelial dysfunction. Studies have confirmed that the stress-induced protein Sestrin2 (SESN2), through the coordinated regulation of the Nrf-2, AMPK, and mTORC1 signaling networks, maintains redox homeostasis and inhibits the endoplasmic reticulum stress-related apoptotic pathway. The loss of its function can significantly exacerbate the oxidative damage of endothelial cells. It is worth noting that in patients with chronic metabolic diseases such as diabetes, the impairment of the endogenous SESN2 homeostasis regulation ability may significantly increase the risk of cardiovascular complications through the continuous activation of endoplasmic reticulum stress.[130] In addition, Nrf-1/Nrf-2, through the silencing mediation of the PPARα/HMGCS2 signaling axis or the activation of the AMPK/NDUFA13 signaling axis, significantly upregulates the expression of PGC-1α, synergistically activates the antioxidant stress pathway (inhibition of NQO1, enhancement of SOD1), inhibits the loss of mitochondrial membrane potential and the accumulation of ROS. At the same time, by reducing the heart weight index, blood glucose and lipid levels, and the expression of pathological markers (ANP, BNP, TGF-β1), it reverses the apoptosis and oxidative damage of myocardial cells in diabetic cardiomyopathy, and ultimately achieves the myocardial protective effect.[131,132]

The latest research shows that Nrf-2 exhibits multi-dimensional regulatory characteristics in the pathological process of heart diseases. In terms of neonatal heart injury, Nrf-2 regulates mitochondrial quality control through the antioxidant and anti-apoptotic effects mediated by the polyamine spermidine. It increases the number of mitophagosomes to reduce dysfunctional mitochondria. At the same time, it regulates biogenesis by inhibiting the expression of SIRT-1, PGC-1α, Nrf-2, and TFAM, and coordinates the dynamics of fission/fusion (decreasing the expression of DRP1 and increasing the level of MFN2). Ultimately, it improves the structural and functional abnormalities of myocardial mitochondria and alleviates neonatal heart injury.[133] In terms of myocardial injury in sepsis, Nrf-2 regulates the miR-122-5p/GIT1 molecular network by activating the HO-1/NQO-1 signaling axis, significantly inhibiting oxidative stress, the inflammatory cascade, and the apoptotic pathway, thus playing a cardioprotective role in the sepsis-related myocardial injury model.[134] The core of its mechanism lies in blocking the pathological process of lipopolysaccharide-induced myocardial cell injury through targeting the miRNA regulatory network. In terms of myocardial infarction, the nanovesicles Carex isolated from carrots exert significant antioxidant and anti-apoptotic effects by activating the Nrf-2 signaling pathway and its downstream related signaling molecules such as HO-1 and NQO-1, providing new ideas for the treatment of myocardial infarction.[135] In terms of cardiac dysfunction caused by metabolic syndrome, the downregulation of Nrf-2 will impair the cardioprotective effect of metformin in regulating ferroptosis.[136] In terms of atrial fibrosis, Nrf-2 improves atrial fibrosis during antithrombotic treatment for atrial fibrillation by regulating the activity of CYP2C9.[137] The molecular commonalities across the above disease models indicate that, as the core hub of cardioprotection, Nrf-2 provides a key target for precision cardiovascular treatment by integrating the redox homeostasis, organelle quality control, and epigenetic regulation networks.

Potential Cardiovascular Therapeutic Strategies Targeting the Nrf Family

Based on the central role of the Nrf family in regulating redox homeostasis, metabolic adaptation, and inflammatory responses, therapeutic strategies targeting this pathway have become a research hotspot in the intervention of CVDs. Current research focuses on developing precise intervention methods from multiple dimensions, such as molecular activation, genetic regulation, multi-pathway coordination, and environmental interaction. The aim is to overcome the non-specificity and compensatory feedback defects of traditional antioxidant therapies. The following systematically

elaborates on innovative paradigms based on drug development, genetic and epigenetic interventions, combination therapies, and lifestyle interventions, and explores their application potential and translational bottlenecks in cardioprotection.

Drug Development (Pharmacological Activators)

Natural Drugs Developed for the Nrf-2 Pathway

Recent studies have confirmed that natural bioactive components that target and regulate the Nrf-2 signaling pathway have significant application prospects in the prevention and treatment of CVDs. These compounds specifically activate the Nrf-2 transcription factor, significantly upregulate the expression of antioxidant enzymes such as HO-1 and NQO1, and simultaneously downregulate the activity of pro-inflammatory factors such as NF-κB. As a result, they can effectively improve the oxidative stress state and inhibit the inflammatory response, exerting a remarkable protective effect on the function of myocardial cells and vascular endothelium. According to the characteristics of their chemical composition, currently, natural activators of Nrf-2 are mainly divided into two categories: ① Single bioactive components (monomeric compounds); ② Composite extracts (multi-component systems) (For the specific classification and mechanism of action, please refer to Table 1).

Synthetic Drugs Developed for the Nrf-2 Pathway

In recent years, synthetic drugs targeting the Nrf-2 signaling pathway have made significant progress in the treatment of CVDs. Through mechanisms such as the synergistic activation of the endogenous antioxidant defense system (such as NQO1, GCL, etc). and the inhibition of the activation of the NLRP3 inflammasome, these drugs have demonstrated remarkable cardioprotective effects in various pathological models, including myocardial ischemia-reperfusion injury and myocardial infarction. These effects include multiple aspects such as improving the survival rate of myocardial cells, reducing oxidative stress damage, and inhibiting the inflammatory response (see Table 2 for details).

Other Drugs Developed for the Nrf-2 Pathway

In addition to traditional natural drugs and synthetic drugs, novel therapeutic modalities based on the Nrf-2 pathway have demonstrated unique advantages in the cardiovascular field. The current research hotspots mainly include: ① Nanodrug delivery systems (such as polymer nanoparticles loaded with Nrf-2 activators), which precisely regulate the pathway activity by enhancing the targeting ability and bioavailability; ② Microbial intervention therapies (such as fecal microbiota transplantation), which regulate the Nrf-2-mediated oxidative stress defense through the gut-heart axis. These innovative therapies provide new ideas for the precision treatment of CVDs (For specific research progress, please refer to Table 3).

Gene Therapy (Genetic and Epigenetic Interventions)

Gene therapy technology has opened up a new pathway for the treatment of CVDs. Existing studies have shown that the protective effect of VO-OHpic on endplate chondrocytes can be significantly reversed by transfecting Nrf-2 siRNA, which suggests that gene transfection technology has the potential in regulating the expression of Nrf family members.[170] The cardioprotective effect of beige adipocyte-derived FGF21 strictly depends on the Nrf-2 signaling pathway. When gene silencing technology is used to knock down Nrf-2, the effects of FGF21-mediated antioxidant stress, anti-apoptosis, and improvement of mitochondrial function are significantly inhibited.[171] It is worth noting that in the Nrf-2 gene knockout mouse model, the cardioprotective effects of Prunella vulgaris and ursolic acid are completely lost, accompanied by the downregulation of GPX4 protein expression, further confirming the central regulatory role of Nrf-2 in this protective mechanism.[172]

In addition, studies have also confirmed that ferroptosis induced by iron overload is closely related to the heart injury caused by SiO_2. Targeted intervention of ferroptosis by reducing iron accumulation or inhibiting lipid peroxidation may effectively counteract the cardiotoxicity caused by SiO_2 through regulating the Nrf-2 pathway.[173] Therefore, we speculate that introducing genes of Nrf family members into myocardial cells through gene transfection technology can effectively increase the expression levels of Nrf family members in myocardial cells, thereby exerting a cardioprotective effect.

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Table 1 Overview of Natural Drugs Targeting the Nrf-2 Pathway

Drug	Disease Types	In Vivo/In Vitro	Subjects	Protocols	Effects		References
					Promotion Effects	Inhibition Effects	
Single Compounds							
Astragaloside IV	Heart Failure	In Vivo/In Vitro	Wistar rats (heart failure model)/H9C2 cells (doxorubicin)	1.0 mg/kg, *i.p.*, 9 weeks/ 50,100 μmol/L, 24 h	EF (myocardial contractility improved); mitofusin1, mitofusin2 (mitochondrial dynamics enhanced); Nrf-2, HO-1 (Nrf-2 pathway activated).	TUNEL-positive cells (apoptosis inhibited); DRP1, low membrane potential cells (mitochondrial function improved).	[138]
Astragaloside IV	Cardiac Dysfunction	In Vivo	Male C57BL/6 mice (doxorubicin)	40 mg/kg, *i.g.*, 4 weeks	LVEF, LVFS (cardiac function improved); Myocardial cell area, HW/BW ratio (ultrastructure ameliorated); SOD, GSH (antioxidant); Nrf-2, HO-1 (Nrf-2 pathway activated).	LVIDd, LVIDs (cardiac structure improved); BNP, CK-MB, cTnI, LDH (cardiac injury reduced); IL-1β, IL-18, MDA (antioxidant/ anti-inflammatory); NLRP3, ASC, caspase-1, GSDMD (pyroptosis inhibited).	[139]
Piceatannol	Myocardial Ischemia/ Reperfusion Injury	In Vivo/In Vitro	Male C57BL/L6 mice (myocardial ischemia/ reperfusion model)/AC16 cell (hypoxia-reoxygenation)	10, 20, 40 mg/kg, *i.p.*/10, 20, 40 μM, 12 h	Nrf-2 (Nrf-2 pathway activated); FPN1 (iron efflux function improved).	Intracellular ferrous ions (iron overload); lipid peroxidation products (oxidative damage alleviated); TfR-1 (iron uptake inhibited).	[140]
Naringenin	Myocardial Ischemia/ Reperfusion Injury	In Vivo/In Vitro	SD rats (left anterior descending coronary artery with a slipknot)/H9C2 cells (Erastin)	10, 50, 60 mg/kg/d, *i.g.*, 7 days preoperatively/20, 40, 80 μM, 24 h	GSH, SOD (lipid peroxidation reduced); Nrf-2, SLC7A11, GPX4, FTH1, FPN1 (ferroptosis improved).	CPK, LDH (pathological damage alleviated); IL-6, IL-1β, TNF-α, MPO, MDA, ROS (inflammation and lipid peroxidation reduced); Total iron, Fe^{2+}, NOX1 (ferroptosis improved).	[141]
Wogonin	Cardiac Hypertrophy	In Vivo/In Vitro	C57BL/6 mice (transverse aortic constriction) /H9C2 cells, neonatal rat cardiomyocytes (AngII)	10 mg/kg/day, *i.p.*/1, 2.5, 5, 10, 20, 40, 60, 80 μM, 48 h	SOD (antioxidation); Nrf-2, HO-1, NQO-1 (Nrf-2 pathway activated).	IVSd ↓ 15.44%, IVSs ↓ 17.59%, LVPWd ↓ 12.74%, LVPWs ↓ 13.58%, LVIDd ↓ 22.41%, LVIDs ↓ 26.28% (cardiac myocyte hypertrophy inhibited); MyHC-β (cardiac myocyte hypertrophy inhibited); MDA, ROS (antioxidation); Keap-1 (Nrf-2 negative regulators inhibited).	[142]
Galangin	Cardiorenal Dysfunction and Hypertrophy	In Vivo	Male SD Rats (hypertension Model)	30, 60 mg/kg, orally, 4 weeks	CAT ↑ 48.80% (antioxidation); Nrf-2, HO-1 (Nrf-2 pathway activated).	Superoxide ↓ 45.09%, MDA ↓ 72.39% (antioxidation); ACE, AngII (circulating renin-angiotensin system improved); Nox-4, AT1R, TGF-β1, Col-1 (myocardial fibrosis improved).	[143]
Quercetin	Myocardial Infarction Adverse Remodeling	In Vivo	Wistar albino male rats (left anterior descending coronary artery ligation)	50 mg/kg, orally, 30 days	Nrf-2, SOD, GSH, smad7, BMP7 (antioxidant, anti-inflammatory, antifibrotic).	ROS, AngII, NF-κB p65, TGF-β1, α-SMA, total/phospho-smad3 (antioxidant, anti-inflammatory, antifibrotic).	[144]
Punicalagin	Myocardial Infarction	In Vivo	Male wistar rats (isoproterenol)	25, 50 mg/kg, orally, 14 days	CAT, SOD (antioxidant); Bcl-2 (anti-apoptosis); Nrf-2, HO-1 (Nrf-2 pathway activated).	CK-MB, cTnI, LDH, MDA, PCO, NO, 8-OHdG, TNF-α, NF-κB, IL-6, IL-1β, iNOS (antioxidant); Bax, caspase-3 (anti-apoptosis).	[145]
Fucoidan	Cardiotoxicity	In Vivo/In Vitro	Male C57BL/6 mice (doxorubicin)/HL-1 mouse cardiomyocyte cell line (doxorubicin)	200 mg/kg, *i.g.*, 12 days/0, 5, 10, 25, 50, 75, 100 μg/mL, 24 h	GSH, TfR1, FTH1, GPX4 (ferroptosis inhibited); Nrf-2 (Nrf-2 pathway activated).	CK, CK-MB, LDH, LDH-isoenzymes (myocardial injury reduced); Myh7 (cardiac hypertrophy reduced); ROS, MDA, PTGS2, HO-1 (ferroptosis inhibited).	[146]
Aucubin	Cardiotoxicity	In Vivo/In Vitro	C57BL/6 mice (doxorubicin)/H9C2, MCF-7, HepG2 cells (doxorubicin)	10, 20 mg/kg/day, *i.p.*, 28 days/0.1, 1, 5, 10, 20, 50, 100 μM, 24 h	SOD (antioxidation/ mitochondria protected); Bcl-2 (anti-apoptosis); Beclin-1 (autophagy improved); Nrf-2, HIPK2 (Nrf-2 pathway activated and autophagy promoted).	CK-MB, LDH (myocardial injury reduced); ROS, 8-OHdG, MDA (antioxidation/ mitochondrial protected); Bax (anti-apoptosis); LC3, P62 (autophagy promoted).	[147]

Lycopene	Cardiotoxicity	In Vivo/In Vitro	Male C57BL/6J mice (doxorubicin)/H9c2 cells, rat myoblast cell line, AC16 cells, human myocardial cell line (doxorubicin)	40 mg/kg/day, *i.v.*, 30 days/10 μM, 24 h	CAT, SOD2, Bcl-2 (oxidative stress and apoptosis alleviated); mitochondrial membrane potential, GSH, MFN1 (mitochondrial dysfunction in heart failure alleviated); SLC17A1, SLC25A34, ACSL4, Nrf-2, GPX-1, GPX-4 (ferroptosis alleviated via Nrf-2 activation).	CK-MB, LDH, HBDH (cardiac dysfunction alleviated); ALP, ALT, AST (liver function improved); ANP, BNP, MMP-2, MMP-9, TGF-β, α-SMA (cardiac fibrosis alleviated); ROS, 4-HNE, 8-OHdG, p53, Bax, Bad, cleaved-Caspase-3 (oxidative stress and apoptosis alleviated); IL-6, TNF-α, PPARγ, F4/80, MCP-1, IL-1β, IL-33, HMGB1, MDA, FUNDC1, DRP1, FIS1(inflammation and mitochondrial dysfunction alleviated); ALOX12, LCN2, TRIM21, TRIM34a (ferroptosis alleviated via Nrf-2 activation).	[148]
Ophiopogon japonicus polysaccharide	Cardiotoxicity	In Vitro	Human cardiomyocyte AC16 cell line (doxorubicin)	50, 100, 200 μg/mL, 6 h	ATP, mitochondrial membrane potential (mitochondrial dysfunction in myocardial ferroptosis alleviated); Nrf-2, GPX4 (myocardial ferroptosis alleviated via Nrf-2-activated pathway).	LDH, CK-MB, cTn-I, MDA, ROS (antioxidant); TfR1, Fe^{2+} (iron accumulation in myocardial ferroptosis reduced).	[149]
Silybin	Cardiotoxicity	In Vivo	Juvenile carp (avermectin)	400 mg/kg, fed, 30 days	CAT, GSH, T-AOC, SOD, GSH-px, Nrf-2 (cardiac oxidative stress alleviated);TGF-β1, IL-10 (anti-inflammation); Bcl-2 (cardiac cell apoptosis reduced via mitochondrial pathway).	CK, CK-MB (cardiac injury alleviated); ROS, MDA, Keap1 (cardiac oxidative stress mitigated); TNF-α, IL-6, iNOS, IL-1β, NF-κB (cardiac inflammation relieved); GRP78, ATF6, CHOP, IRE1, PERK, EIF2a (cardiac endoplasmic reticulum stress alleviated); Bax, Caspase-3, Caspase-9, Cytochrome C, DRP1 (cardiac cell apoptosis reduced via mitochondrial pathway); ATG5, LC3-II, PINK1, PARKIN, BNIP3 (cardiac mitophagy reduced).	[98]
Epigallocatechin-3-gallate	Endothelia Cells Injury	In Vitro	HUVECs (ethanol)	100, 200 μM, 12 h	Bcl-2 (anti-apoptosis); mitochondrial membrane potential (mitochondrial damage alleviated); Nrf-2 (Nrf-2 pathway activated).	Bax, cleaved-caspase-3 (antiapoptosis); ROS (antioxidant); NF-κB, TNF-α, IL-1β, IL-6 (anti-inflammatory).	[150]
Extracts Containing Multiple Compounds							
Boswellia serrata Gum Resin Extract	Autoimmune Myocarditis	In Vivo	Male SD rats (autoimmune myocarditis model)	10, 50, 100 mg/kg, orally, 30 min pre-Carrageenan injection; 100 mg/kg/day, orally, 21 days	IL-4, IL-10 (anti-inflammatory); Nrf-2, HO-1, SOD (Nrf-2 pathway activated/antioxidant).	CK-MB, LDH (cardiac injury reduced); α-SMA, TGF-β (fibrosis/inflammation process reduced); TNF-α, IL-6, IL-17, IL-2 (pro-inflammatory cytokines reduced); CD4, CD8, CD45, CD11β (inflammatory cells alleviated).	[151]
Xinshuaining preparation	CVDs	In Vivo/In Vitro	Adult SD rats/H9c2 cells (H_2O_2)	31.2 g/(kg.d), *i.g.*, 7 days/10% medicated serum	Cell viability, SOD, GSH-Px, mitochondrial membrane potential, p-PI3K, p-Akt, Nrf-2 (antioxidant).	Cell apoptosis rate, MDA, ROS (antioxidative stress and antiapoptosis).	[152]
Poly herbal Formulation	Diabetic Cardiomyopathy	In Vivo	Male albino wistar rats (streptozotocin and nicotinamide administration)	250, 500 mg/kg/BW, orally, 45 days	Nrf-2, HO-1 (Nrf-2 pathway activated); SOD RNA, CAT RNA (cardiac oxidative stress alleviated).	TNF-α (anti-inflammatory); NF-κB (antioxidative stress).	[153]
Phenolics Extracted from Jasminum Sambac	Diabetic Cardiomyopathy	In Vivo/In Vitro	Wistar albino rats (alloxan)	250, 500 mg/kg, orally, 6 weeks	Insulin ↑ 31.76%, HDL ↑ 19.58%, GPx ↑ 18.35%, CAT ↑ 45.98%, Bcl-2, Nrf-2, HO-1 (antioxidative stress and antiapoptosis)	Glucose ↓ 19.94%, glycosylated hemoglobin ↓ 20.28%, cholesterol ↓ 19.37%, triglycerides ↓ 26.18%, ALT ↓ 18.75%, AST ↓ 15.10%, TBRAS ↓ 29.80%, SOD ↓ 4.94%, LDH ↓ 17.42%, caspase-3, Bax, cTnI, proBNP, CK-MB, IMA (cardiac function improved).	[154]
Qishen Granule	Cardiotoxicity	In Vivo/In Vitro	Male C57 BL/6 mice (doxorubicin)/H9c2 cells (doxorubicin)	2.5, 5 g/kg, *i.v.*, 12 days/800μg/mL, 24h	GSH, Nrf-2, GPX4, FTH1, FPN, FTMT (ferroptosis alleviated).	CK-MB, LDH (antiapoptosis); MDA, ROS, mitochondrial vacuolization, outer mitochondrial membrane, mitochondrial cristae (ferroptosis relieved).	[155]

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Table 2 Overview of Synthetic Drugs Targeting the Nrf-2 Pathway

Drug	Disease Types	In Vivo/In Vitro	Subjects	Protocols	Effects		References
					Promotion Effects	Inhibition Effects	
Dexmedetomidine	Myocardial Ischemia/ Reperfusion Injury	In Vivo/In Vitro	Male SD rats (langendorff preparation)/H9c2 cells (hypoxia/reoxygenation model)	10 nM, perfusion, 30 min/10 nM, 1 h	GSH, SOD (antioxidant); Nrf-2 (nuclear translocation promoted); mitochondrial morphology (antiapoptosis); HO-1, SLC7A11, GPX4 (SLC7A11/GPX4 pathway activated); AMPK, GSK-3β (AMPK/GSK-3β pathway activated).	LDH (antiapoptosis); Fe^{2+}, ROS, MDA, 4-HNE (ferroptosis inhibited).	[156]
Acacetin	Myocardial Ischemia/ Reperfusion Injury	In Vivo	Male SD rats (myocardial ischemia/ reperfusion model)	10 mg/kg, neck injection, twice daily, 7 days	LVEF, LVFS (cardiac function enhanced); SOD (antioxidant); IL-10 (anti-inflammatory); Bcl-2 (anti-apoptotic); Nrf-2, HO-1 (Nrf-2 pathway activated).	LVIDs (left ventricular end-systolic diameter reduced); Inflammatory cell infiltration, myocardial fibrosis, collagen 1/3 (cardiac pathological changes alleviated); MDA (oxidative stress reduced); TLR4, IL-6 (anti-inflammatory); Bax (anti-apoptotic).	[157]
N -N-Butyl Haloperidol Iodide	Myocardial Ischemia/ Reperfusion Injury	In Vivo	Male C57BL/6N mice (myocardial ischemia/ reperfusion model)	0.1, 0.2, 0.4 mg/kg, *i.v.* injection 5 min before reperfusion	Nrf-2, HO-1, NQO-1 (Nrf-2 pathway activated and oxidative stress alleviated); SIRT1 (Nrf-2 regulated).	LDH, CK- MB, CK (myocardial enzymes leakage reduced).	[158]
CBR-470-1	Myocardial Ischemia/ Reperfusion Injury	In Vivo	Wild-type C57BL/6J mice (myocardial ischemia/reperfusion model)	2, 3, 6 mg/kg, *i.p.*, 24 h,	Bax, GSH, ATP (anti-apoptosis, anti-inflammation); Nrf-2, NQO1, GCLC, SOD1, PRDX1, GPX4, SLC7A11 (ferroptosis inhibited).	ROS, Bax/Bcl-2, NOX2, MDA, IL-1β, IL-6, TNF-α (anti-apoptosis, anti-inflammation); p53, NLRP3 (ferroptosis inhibited).	[159]
Costunolide	Diabetic Cardiomyopathy	In Vivo/In Vitro	Male C57BL (STZ)/6 mice/H9c2 cells (glucose)	20 mg/kg, orally, once every 2 days, eight weeks/2.5–20 μM, 48 h	Nrf-2, HO-1 (antioxidant).	LDH, CK-MB (cardiac injury protected); BNP, cardiac structure abnormalities (reversed); Collagen fibers, Collagen I, TGF-β, MyHC-β (myocardial fibrosis reduced); Col1a1, Col4a1, Myh7 (myocardial hypertrophy reduced); macrophages infiltration, IκB-α, p-TBK1, p-P65, MCP-1, TNF, IL-6, IL-1β, iNOS, CCL2, ROS, p38-MAPK (anti-inflammation).	[160]
L-Arginine	Diabetic Cardiomyopathy	In Vitro	H9c2 cardiomyocytes (glycated human serum albumin)	40, 80, 160, 320, 640 mM, dark, 8 days, 37 °C	NO, SOD, CAT, GSH, GLO I, GLO II (antioxidant); Nrf-2, GLO I, GLO II, HO-1, NQO1 (Nrf-2 pathway activated).	ROS (antioxidant); Keap1 (Nrf-2 pathway activated).	[161]
Agomelatine	Acute Myocardial Infarction	In Vivo	Male wistar rats (ISO-induced, 100 mg/kg *i.p.* on days 11 and 12)	80 mg/kg/day, *i.g.*, 12 days	SOD, GSH (antioxidant); IL-10 (anti-inflammatory); Nrf-2, HO-1 (Nrf-2 pathway activated).	CK-MB, AST, LDH, ALP (tissue injury relieved); MDA (antioxidant); cGMP, NOX2, NOX, TNF-α (anti-inflammatory); iNOS, caspase-3 (anti-apoptosis).	[162]
3'-daidzein sulfonate	Myocardial Infarction	In Vivo/In Vitro	female wistar rats (left anterior descending coronary artery ligation)/HL-1 cell (mouse atria cells)	1, 2 mg/kg/5, 10 μmol/mL	SOD, GSH (antioxidant); Nrf-2, HO-1, Bcl-2 (Nrf-2 pathway activated and anti-apoptotic).	Myocardial infarction area (fibrosis reduced); cTnI, CK-MB, LDH (myocardial injury alleviated); MDA (antioxidant); Keap1, Bax, cleaved-caspase-3, caspase-3 (Nrf-2 pathway activated and anti-apoptotic).	[163]
Abatacept	Myocardial Infarction	In Vivo	Male wistar albino rats (chemically induced myocardial necrosis; ischemia-reperfusion model)	2.5, 5, 10 mg/kg, subcutaneously, 21 days	GSH, SOD, CAT (antioxidant); Bcl-2 (anti-apoptosis); Nrf-2, HO-1 (Nrf-2 pathway activated).	MDA (antioxidant); CK-MB, LDH (cardiac injury alleviated); Bax, caspase-3 (anti-apoptosis); TNF, IL - 6 (anti-inflammatory); p38, JNK MAPK, PARP (MAPK pathway blocked).	[164]

Sulforaphane	Cardiotoxicity	In Vivo	Male adult wistar rats (cuprizone)	2 mg/ kg, *i.p.*, 14 days	TAC, Lipid peroxidation, CAT (antioxidant); Nrf-2 (antioxidant and anti-inflammatory).	cTn1, AST, ALT, ALP (antioxidation); IFN-γ, IL-1β (anti-inflammatory).	[165]
Bardoxolone Methyl	Cardiotoxicity	In Vivo/In Vitro	Male SD rats (doxorubicin)/H9c2 cells (doxorubicin)	10 mg/kg, *i.p.*, 6 weeks/30, 40 μM, 24 h	Nrf-2, HO-1, NQO1, SOD (Nrf-2 pathway activated and antioxidant); TRX (cardiac pyroptosis reduced).	BNP (cardiac injury and fibrosis alleviated); MDA, ROS (antioxidation); TXNIP, NLRP3, cleaved GSDMD, IL-1β, IL-18 (cardiac pyroptosis reduced).	[166]
Thymoquinone	Cardiotoxicity	In Vivo	Male C57BL/6 mice (doxorubicin)	10, 20 mg/kg/d, *i.p.*, 2 weeks	NQO1, GSH, T-AOC (oxidative stress alleviated); Nrf-2, HO-1, GPX4, FTH1 (Nrf-2 pathway activated, ferroptosis reduced).	LDH, CK-MB, BNP (cardiomyocyte injury and mitochondrial damage alleviated); COX-2, NOX4, MDA (oxidative stress alleviated); Fe^{2+} (myocardial iron level reduced).	[167]
Sodium Selenite	Vascular Endothelial Cytotoxic Injury	In Vivo/In Vitro	Male SD rats /HUVECs (silver nanoparticles)	0.2 mg/kg/day, *i.p.*, 7 days/1, 2, 4, 6, 8, 10 μM, 24 h	eNOs (vascular endothelial cells injury improved); ZO-1 (vascular dysfunction protected); IL-10 (anti-inflammatory); GSH, SOD (antioxidant); Nrf-2, HO-1 (Nrf-2 pathway activated).	ICAM-1, VCAM-1 (vascular endothelial injury improved); TNF-α, IL-1β, IL-6 (anti-inflammatory); MDA, ROS (antioxidant); NLRP3, CD31, ASC, Caspase-1, IL-18, IL-1β (NLRP3 inflammasome activation inhibited); HMGB1, NF-κB, TLR4, TNF-α (HMGB1/NF-κB pathway inhibited).	[168]

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Table 3 Overview of Other Drugs Targeting the Nrf-2 Pathway

Drug	Disease Types	In Vivo/In Vitro	Subjects	Protocols	Effects		References
					Promotion Effects	Inhibition Effects	
Hypoxic ExtraCellular Vesicles From hiPSCs	Myocardial Ischemia/ Reperfusion Injury	In Vitro	Cardiomyocytes (oxygen-glucose deprivation/ reoxygenation model)	3% physiological hypoxia, 5% O_2, 21% atmospheric O_2	HO-1, SOD2, GSTP1, CAT (antioxidation); p-Akt, p-ERK, Bcl-2 (pro-survival pathway triggered); calcium signaling and contractile ability (restored); PRDX1, PRDX6, GSTP1 (Nrf-2 pathway antioxidant response stimulated).	ROS, TNF-α, IL-6, IL-1β, TLR4 (anti-inflammatory); ROS, p-AMPK, Bax (pro-survival pathway triggered).	[169]
Acid-Triggered Cascaded Responsive Supramolecular Peptide	Myocardial Ischemia/ Reperfusion Injury	In Vivo/In Vitro	Male C57BL/6 mice (myocardial ischemia/ reperfusion model)/ H9c2 cells, RAW264.7 macrophages (LPS)	100 μL, *i.p.*, 1 min before reperfusion/40 μM, 24 h	Nrf-2 (Nrf-2/Keap-1 complex bound and activated); HO-1, SLC7A11, GPX4, GSH (ferroptosis inhibited via Nrf-2/HO-1/GPX4 pathway); mitochondrial membrane potential (function improved and antiapoptosis); CD206/CD68 (anti-inflammatory).	ROS, Fe^{2+} (iron deposition inhibited); mtROS, mtLPO, mPTP, Cytochrome c (mitochondrial function improved and antiapoptosis); cTnT, CK-MB (myocardial injury alleviated); iNOS, NLRP3, TNF-α, IL-1β, iNOS, CD68 (anti-inflammatory).	[68]
Momordica Charantia L.-derived Exosome-like Nanovesicles	Cardiotoxicity	In Vivo/In Vitro	Male C57BL/6J male mice (doxorubicin)/ H9c2 cells, MCF-7 cells (doxorubicin)	800-1200 μg/kg, *i.v.*, 24 h/0, 0.5, 5, 10, 25 μg/mL, 24 h or 48 h	Cyclin D1, Cyclin E1 (cell cycle arrest blocked); Ki-67 (cell proliferation enhanced); p62 (autophagosome accumulation reduced); Nrf-2, HO-1, NQO1, CAT (Nrf-2 pathway activated).	cTnT, CK-MB (cardiac protection); Cleaved caspase-3, Cleaved caspase-7, Cleaved PARP (antiapoptosis); ROS, MitoSOX, γ-H2A (oxidative stress alleviated and mitochondria structure maintained); LC3B II (autophagosomes accumulation reduced); Keap1 (Nrf-2 pathway activated).	[87]
Fecal Microbiota Transplantation	Cardiotoxicity	In Vivo	Male C57BL/6J mice (doxorubicin)	Orally, four weeks	SOD (oxidative stress alleviated); MFN2, Mitochondrial respiratory chain complexes I/III (mitochondrial fission-fusion dynamics and function regulated);Nrf-2, NQO1, HO-1 (Nrf-2 pathway activated).	MDA (oxidative stress alleviated); p-DRP-S616 (mitochondrial fission-fusion dynamics and mitochondrial function regulated).	[73]

Gene therapy has attracted much attention due to its strong targeting ability and long-lasting effect. However, it is still in the clinical research stage, and its safety and effectiveness still need to be verified through further clinical trials.

Combination Therapy

Interestingly, the triple therapy of mitochondrial transplantation combined with mitoquinone and melatonin effectively improved mitochondrial function and biogenesis by enhancing the Nrf-2/SIRT-1/PGC-1α signaling pathway, providing significant cardioprotection for the hearts of aged rats and markedly reducing myocardial ischemia-reperfusion injury.[174] The combined treatment of novel solid lipid nanoparticles encapsulated nanoquercetin (N-QCT) and curcumin significantly upregulates the mRNA and protein expression of downstream antioxidant enzymes (SOD1, GPX, HO-1) through the synergistic activation of the Nrf-2 signaling pathway. Meanwhile, it dual-regulates the TGF-β/NOX/Erk1/2 and ROS/Nrf-2 pathways, inhibits the phosphorylation of Erk1 and reduces the generation of ROS, thus exerting a cardioprotective effect in the treatment of atherosclerosis.[175] In addition, the combination of bisoprolol and trimetazidine significantly reduces the release of inflammatory mediators and inhibits the apoptosis of myocardial cells by precisely regulating the PI3K/GSK-3β/Nrf-2/HO-1 and NF-κB/iNOS signaling networks, effectively alleviating the acute myocardial injury induced by arsenic trioxide.[176]

In addition, the supplementation of ginger extract and Omega-3 fatty acids is regarded as one of the promising strategies for improving diabetic cardiomyopathy. They can activate the Nrf-2 signaling pathway, inhibit the NF-κB signaling pathway, reduce the expression of inflammatory factors such as TRPM2 and TRPV2, and balance the indices of apoptotic factors such as Bax/Bcl-2.[177] More interestingly, when melatonin, NMN, and ubiquinol are used alone or in combinations of two, they do not show significant cardioprotective effects. However, when these three are used in combination, Nrf-2 is activated and plays a role in improving myocardial function by upregulating the SIRT-1/PGC-1α/Nrf-2/TFAM signaling pathway. Specifically, it reduces the infarct size and CK-MB levels after myocardial ischemia/reperfusion, improves mitochondrial function, and promotes the recovery of mitochondrial biogenesis genes.[178] These synergistic effects highlight the therapeutic potential of the combined targeting of the Nrf family by natural compounds in CVDs.

Lifestyle Intervention

In addition to drug therapy and gene therapy, lifestyle intervention is also an important approach to enhancing the activity of Nrf family members. Lifestyle intervention, by regulating redox homeostasis, has become a non-pharmacological strategy for the targeted activation of the Nrf family. During normal exercise training, as a core antioxidant regulatory factor, Nrf-2 initiates its protective mechanism after being activated by α1AMPK. On the one hand, it directly upregulates the expression of antioxidant molecules such as HO-1 and Ucp-2, enhancing the ability of cells to scavenge excessive ROS. At the same time, it synergistically inhibits the activity of phagocytic NADPH oxidase (NOX-2), reducing the generation of oxidative stress products at the source, thus maintaining the dynamic balance between NO and ROS. On the other hand, Nrf-2 maintains the coupled state of eNOS, preventing the pathological mode conversion of superoxide anions caused by its abnormal function, ensuring the normal synthesis of NO to exert an endothelial protective effect. Furthermore, by inhibiting the expression of pro-inflammatory factors such as TNF-α and IL-1β, it blocks the vicious cycle between oxidative stress and the inflammatory response, ultimately achieving comprehensive regulation of vascular homeostasis.[179]

Dietary interventions can exert significant cardiovascular protective effects by targeting and activating the Nrf-2 signaling pathway. Studies have shown that olive oil by-product Pâté can specifically activate the Nrf-2 pathway, upregulate the expression of antioxidant enzymes such as HO-1 and NQO1, thereby effectively improving lipid metabolism disorders and inhibiting the formation of atherosclerotic plaques.[180] A crossover trial involving 19 participants demonstrated that after 2 months of daily administration of olive oil by-product Pâté tablets containing 30 mg of hydroxytyrosol, the plasma Nrf-2 level in the subjects increased significantly by 88.9%, while total cholesterol and low-density lipoprotein cholesterol both decreased by 10.8 mg/dL, the level of proinflammatory protein MCP-1 decreased by 9.0 pg/mL, and the response of leukocytes to exogenous oxidative stress was reduced by 12.8%. These results suggest that this dietary intervention can improve cardiovascular metabolic risk by activating the Nrf-2 pathway.

Furthermore, dietary capsaicin can significantly inhibit the process of ferroptosis by coordinately regulating the Nrf-2/HMOX1 and TRPV1 pathways, thereby alleviating diabetic myocardial infarction injury.[181] Long-term intake of green mushrooms can delay age-related cardiovascular dysfunction and promote healthy aging through activating the Nrf-2/HO-1 axis.[182] These findings collectively confirm that dietary strategies, via the Nrf-2-mediated antioxidant-anti-inflammatory network, provide a scientific basis and translational potential for nutritional intervention in CVDs.

Current Status and Challenges of Nrf Family in Clinical Practice

Although the mechanistic research and translational potential of the Nrf family in CVDs have been widely confirmed, their application in daily clinical practice remains in the exploratory stage. At present, the expression levels of Nrf family members (eg, plasma concentration of Nrf-2, localization of Nrf-3 in myocardial tissue) have not been incorporated into the standard indicators for routine diagnosis or prognostic evaluation of CVDs. This is mainly due to the lack of standardized detection methods (such as selection of sample types and determination of detection thresholds) and large-scale clinical validation data. At the intervention level, among strategies targeting the Nrf pathway, dietary interventions (eg, olive oil by-products rich in hydroxytyrosol) have been used as auxiliary measures in some health management scenarios due to their high safety and easy popularization. However, standardized clinical recommendation protocols for specific diseases (eg, coronary heart disease, heart failure) have not yet been established. In contrast, synthetic drugs targeting Nrf-2 (such as omega-3 fatty acid derivatives and bardoxolone methyl), despite showing cardioprotective effects in animal experiments and early-phase clinical trials, have not been approved for routine treatment of CVDs due to issues related to long-term safety (eg, impacts on renal function) and dosage optimization.

Furthermore, methods for clinically evaluating Nrf pathway activity still need to be improved: currently, they mostly rely on detecting plasma levels of antioxidant enzymes (eg, HO-1, NQO1) or gene expression to indirectly reflect its function, and there is a lack of direct tools for monitoring pathway activity. In the future, it will be necessary to define the clinical cutoff values of Nrf indicators through multicenter clinical trials and establish a complete clinical pathway encompassing "detection-intervention-efficacy evaluation" to promote the translation of Nrf-related research from basic studies to routine clinical applications.

Conclusion

As core members of the CNC-bZIP transcription activator family, the Nrf family play a pivotal role in maintaining cardiovascular homeostasis by regulating redox balance, inflammatory responses, mitochondrial function, and programmed cell death (apoptosis, autophagy, and pyroptosis). Among them, Nrf-2, as a key member, significantly alleviates myocardial injury in diseases such as myocardial ischemia-reperfusion injury, atherosclerosis, and heart failure by activating antioxidant genes and phase II detoxifying enzymes, thus serving as a crucial regulatory target for cardiovascular protection. Although Nrf-1 and Nrf-3 have been less studied, their roles in metabolic balance and cellular stress provide supplementary insights into the mechanisms underlying CVDs.

Therapeutic strategies targeting the Nrf family have shown clear potential: natural drugs (eg, Astragaloside IV) and synthetic drugs (eg, Dexmedetomidine) improve disease prognosis by activating Nrf pathways; gene editing and epigenetic interventions provide new approaches for precise regulation of Nrf activity; and combined therapies as well as lifestyle interventions (such as exercise and diet) further expand the scope of clinical applications.

These findings not only reveal the significance of the Nrf family as a core regulator of the "redox-inflammation-mitochondrial function-cell death" network but also provide multi-dimensional targets for the prevention and treatment of CVDs. Future research should focus on strengthening studies on the cell-specific mechanisms of Nrf family members (especially Nrf-3), promoting safety evaluations in clinical translation, and developing individualized therapeutic regimens based on genetic polymorphisms, ultimately achieving the leap from basic research to clinical application.

Prospect

The Nrf family plays an important role in cardiac health. Through mechanisms such as anti-oxidative stress, anti-inflammation, reduction of mitochondrial damage, and regulation of apoptosis, autophagy, and pyroptosis, it protects the heart from damage. In the future, with in-depth research on the Nrf family pathways, it is expected that more novel

therapies for CVDs can be developed, providing more treatment options for patients. Meanwhile, there is a need to further explore the specific mechanisms of action of Nrf family members in different types of CVDs to formulate more precise treatment plans. In addition, strengthening lifestyle interventions to enhance the activity of Nrf family members is also an important approach for preventing CVDs. Future directions include the integration of multi-omics to reveal the cell-specific networks of the Nrf family and individualized treatments based on the gene polymorphisms of the Nrf family. (The complete abbreviations are shown in the Abbreviations).

Abbreviations

α-SMA, alpha-smooth muscle actin; β-TrCP, beta-transducin repeat-containing protein; γ-H2A, gamma-H2A histone; 4-HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxy-2- deoxyguanosine; ACADL, long-chain acyl-CoA dehydrogenase; ACE, angiotensin-converting enzyme; ACSL4, acyl-CoA synthetase long-chain family member 4; ADCY8, adenylate cyclase type VIII; AKR1C3, aldosterone reductase 1C3; Akt, protein kinase B; ALOX12, arachidonate 12-lipoxygenase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AngII, angiotensin II; ANP, atrial natriuretic peptide; AOPP, advanced oxidation protein products; APN, adiponectin; ARE, antioxidant response element; ASC, apoptosis-associated Speck-like protein containing a CARD; AS-IV, astragaloside IV; AST, aspartate aminotransferase; AT1R, angiotensin II type 1 receptor; ATF6, activating transcription factor 6; ATG-5, autophagy-related gene 5; ATP, adenosine triphosphate; BAG3, Bcl-2-associated athanogene 3; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; BDNF, brain-derived neurotrophic factor; Beclin-1, Bcl-2-interacting coiled-coil myosin-like protein 1; BMP4, bone morphogenetic protein 4; BNIP3, BCL2/adenovirus E1B 19 kDa interacting protein 3; BNP, brain natriuretic peptide; BuChE, butyrylcholinesterase; bZIP, basic region leucine zipper; CACNA1G, calcium voltage-gated channel subunit alpha1 G; CAT, catalase; CCL2, Chemokine (C-C motif) ligand 2; CD11b, cluster of differentiation 11b; cGMP, cyclic guanosine monophosphate; CHOP, C/EBP-homologous protein; CK-MB, creatine kinase-muscle brain; CNC, Cap'n'Collar; CO, carbon monoxide; Col-1, type I collagen; COX-2, cyclooxygenase-2; CPK, creatine phosphokinase; CPT1A, carnitine palmitoyltransferase 1A; CRIF1, CR6-interacting factor 1; CRP, C-reactive protein; cTnI, cardiac troponin I; CVDs, cardiovascular diseases; CYP2C9, cytochrome P450 2C9; Cyt-C, cytochrome C; DNMT1, DNA (cytosine-5-)-methyltransferase 1; DOX, doxorubicin; DRP, dynamin-related protein; EF, ejection fraction; EIF2a, eukaryotic translation initiation factor 2A; eNOS, endothelial nitric oxide synthase; ETC, electron transport chain; F4/80, erythrocyte-specific Fc receptor 4/80; FGF21, fibroblast growth factor 21; FIS1, fission 1, mitochondrial; Fizz1, found in inflammatory zone 1; FPN1, ferroportin1; FTH1, ferritin heavy chain 1; FTMT, ferritin, mitochondrial; FUNDC1, FUN14 domain-containing protein 1; GAS5, growth arrest-specific 5; GATA4, GATA-binding protein 4; GCL, glutamate-cysteine ligase; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modifier subunit; GIT1, G protein-coupled receptor kinase-interacting protein 1; GLO, glyoxalase; GPX, glutathione peroxidase; GRP78, glucose-regulated protein 78; GSDMD, gasdermin D; GSH, glutathione; GSK-3, glycogen synthase kinase-3; GSR, glutathione reductase; GST, glutathione-S-transferase; GSTP1, glutathione S-transferase Pi 1; HBDH, hydroxybutyrate dehydrogenase; HCN4, hyperpolarization-activated cyclic nucleotide-gated channel 4; HDAC1, histone deacetylase 1; HIF-1α, hypoxia-inducible factor 1α; HIPK2, homeodomain interacting protein kinase 2; HMGB1, high-mobility group box 1; HMGCS2, 3-hydroxy-3-methyl-glutaryl-coenzyme A synthase 2; HO-1, heme oxygenase-1; HUVECs, human umbilical vein endothelial cells; *i.g.*, intragastrically; *i.p.*, intraperitoneally; *i.v.*, intravenous; ICAM-1, intercellular adhesion molecule 1; IGF2BP2, insulin-like growth factor 2 binding protein 2; IL, interleukin; IMA, ischemia modified albumin; iNOS, inducible nitric oxide synthase; IP-10, interferon-γ-inducible protein 10; IRE1, inositol - requiring enzyme-1; IRF1, interferon regulatory factor 1; IVSd, interventricular septal dimension in diastole; IVSs, interventricular septal dimension in systole; JAK1, Janus kinase 1; Keap1, Kelch-like ECH-associated protein 1; LC3-II, microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine conjugate; LCN2, lipocalin-2; LDH, lactate dehydrogenase; LOOH, lipid hydroperoxide; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systole; LVPWd, left ventricle end-diastolic posterior wall thickness; LVPWs, left ventricle systolic posterior wall thickness; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MFN,

mitofusin; MitoSOX, mitochondrial superoxide indicator; MMP, matrix metalloproteinase; MPO, myeloperoxidase; mPTP, mitochondrial permeability transition pore; mtLPO, mitochondrial lipid peroxidation; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; mtROS, mitochondrial reactive oxygen species; Myh7, myosin heavy chain 7; MyHC-β, myosin heavy chain-β; NAC, N-acetylcysteine; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NDUFV, NADH dehydrogenase (ubiquinone) flavoprotein; NF-κB, nuclear factor-kappa B; NKX2-5, NK2 Homeobox 5; NLRP3, nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3; NLS, nuclear localization signal; NO, nitric oxide; NOX, nicotinamide adenine dinucleotide phosphate oxidase; NQO1, NAD(P)H, quinone oxidoreductase 1; Nrf, nuclear factor erythroid 2-related factor; NRF-1, nuclear respiratory factor 1; OPA1, optic atrophy 1; Ox-LDL, oxidized low-density lipoprotein; OXPHOS, oxidative phosphorylation; P70S60K, ribosomal protein S6 kinase beta-1; Parkin, Parkinson protein 2, E3 ubiquitin-protein ligase; PARP, poly ADP-ribose polymerase; PCO, peroxynitrite; PERK, protein kinase R-like endoplasmic reticulum kinase; PGAM5, phosphoglycerate mutase 5; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PGE2, prostaglandin E2; PINK1, PTEN induced putative kinase 1; Pitx2, paired - like homeodomain transcription factor 2; PKA, protein kinase A; PKCδ, protein kinase C delta; PPAR-γ, peroxisome proliferator-activated receptor gamma; PRDX, peroxiredoxin; PTEN, phosphatase and tensin homolog deleted on chromosome ten; PTGS2, prostaglandin-endoperoxide synthase 2; PUFA, polyunsaturated fatty acids; RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; S100A9, soluble protein 100-A9; SDH, succinate dehydrogenase; SGLT2, sodium-glucose cotransporter 2; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; SHOX2, short stature homeobox 2; SIRT, silent information regulator 2 homolog; SIX1, sinistral-homeobox 1; SLC17A1, solute carrier family 17 member 1; SLC25A34, solute carrier family 25 member 34; SLC7A11, solute carrier family 7 member 11; Smad3, mothers against decapentaplegic homolog 3; SOD, superoxide dismutase; SQSTM1, sequestosome 1; STAT3, signal transducer and activator of transcription 3; T-AOC, total antioxidant capacity; TAD, transcriptional activation module; TBARS, thiobarbituric acid-reactive substances; TFAM, mitochondrial transcription factor A; TfR, transferrin receptor; TGF-β, transforming growth factor-beta; TLR, toll-like receptor; TNF-α, tumor necrosis factor-alpha; TRIM, tripartite motif-containing protein 59; TRPM2, transient receptor potential melastatin 2; TRPV, transient receptor potential vanilloid; TRX, thioredoxin; TXNIP, thioredoxin-interacting protein; Ucp, uncoupling protein; USP, ubiquitin-specific peptidase; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; xCT, Cystine/Glutamate Antiporter; Ym1, chitinase-like protein 3; ZO-1, zonula occludens-1.

Consent for Publication

All authors have given their consent for the publication of this review article. The content of this article has not been published or submitted for publication elsewhere.

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