Current Status and Challenges of NRF2 as a Potential Therapeutic Target for Diabetic Cardiomyopathy

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Summary

Diabetic cardiomyopathy is one of the main causes of heart failure and death in patients with diabetes mellitus. Reactive oxygen species produced excessively in diabetes mellitus cause necrosis, apoptosis, ferroptosis, inflammation, and fibrosis of the myocardium as well as impair the cardiac structure and function. It is increasingly clear that oxidative stress is a principal cause of diabetic cardiomyopathy. The transcription factor nuclear factor-erythroid 2 p45-related factor 2 (NRF2) activates the transcription of more than 200 genes in the human genome. Most of the proteins translated from these genes possess anti-oxidant, anti-inflammatory, anti-apoptotic, anti-ferroptotic, and anti-fibrotic actions. There is a growing body of evidence indicating that NRF2 and its target genes are crucial in preventing high glucose-induced oxidative damage in diabetic cardiomyopathy. Recently, many natural and synthetic activators of NRF2 are shown to possess promising therapeutic effects on diabetic cardiomyopathy in animal models of diabetic cardiomyopathy. Targeting NRF2 signaling by pharmacological entities is a potential approach to ameliorating diabetic cardiomyopathy. However, the persistent high expression of NRF2 in cancer tissues also protects the growth of cancer cells. This “dark side” of NRF2 increases the challenges of using NRF2 activators to treat diabetic cardiomyopathy. In addition, some NRF2 activators were found to have off-target effects. In this review, we summarize the current status and challenges of NRF2 as a potential therapeutic target for diabetic cardiomyopathy.

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Key words: Reactive oxygen species, Diabetes mellitus, Cancer

Diabetes mellitus affects the heart through various mechanisms including metabolic disturbance, subcellular component abnormalities, microvascular impairment, and cardiac autonomic dysfunction.¹⁻³⁾ Eventually, the structure and function of the heart become impaired without coronary artery disease and hypertension, a disorder known as diabetic cardiomyopathy (DCM).⁴⁻⁷⁾ Although ischemic heart disease is the most frequent cause of heart failure and death in diabetic patients, DCM is increasingly recognized as a clinically relevant entity.⁶⁻⁹⁾ It is estimated that about 12% of the diabetic patients develop DCM.¹⁰⁾

The pathogenesis of DCM is predominantly related to the overgeneration of reactive oxygen species (ROS) as well as impaired antioxidant ability in diabetes mellitus.^{1,11)} The transcription factor nuclear factor-erythroid 2 p45-related factor 2 (NRF2, also called Nfe2l2) is a master regulator of cellular redox status and detoxification response.¹²⁾ It plays a vital role in maintaining the oxidative homeostasis by regulating multiple downstream antioxi-

dants. Thus, NRF2 has been proposed to be an attractive target for DCM. Recent studies show that the activation of NRF2 by natural and synthetic substances reduces high glucose-elicited oxidative damage in cultured cardiomyocytes and prevents the development of DCM in animal models of DCM.^{13,14)} As a result, NRF2 has gained great attention as a promising drug target for preventing the development of DCM. On the other hand, the constitutive activation of NRF2 occurs in a variety of cancers, whose prevalence is increased in diabetic patients. The aberrant activation of NRF2 is correlated with cancer progression, chemoresistance, and radioresistance. This “dark side” of NRF2 associated with tumor risk increases the challenges of using NRF2 activators to treat DCM. In this review, we discuss oxidative stress in diabetes mellitus and the significance of NRF2 in myocardial defense against oxidative damage and evaluate several NRF2 activators that receive wide attention. We also discuss the challenges of NRF2 as a potential therapeutic target for DCM.

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Figure 1. Production of ROS in diabetes mellitus. Diabetes mellitus results in mitochondrial dysfunction, nitric oxide synthase (NOS) uncoupling, endoplasmic reticulum (ER) stress, and up-regulates several ROS-generating enzymes, including NAD(P)H oxidase, xanthine oxidase, and lipoxygenase, and cytochrome P450. These organelles or enzymes oxidize molecular oxygen (O_2) to superoxide ($O_2^{\bullet -}$). Under normal conditions, $O_2^{\bullet -}$ can be converted into the less reactive species hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD), which is further reduced into water and oxygen. In addition, superoxide can interact with coupled NOS-generating nitric oxide (NO) to form the stronger reactive species peroxynitrite ($ONOO^-$), which cause tissue damage. Peroxynitrite can also be converted into hydroxyl radicals ($OH^\bullet$).

DCM in Diabetic Patients

According to the World Health Organization, about 422 million adults were diagnosed with diabetes mellitus worldwide in 2016. Moreover, the prevalence of diabetes mellitus has been rapidly increasing globally, especially in middle- and low-income countries.^{15,16} Diabetes mellitus comprises two broad etiopathogenetic categories: type 1 (T1DM) and type 2 diabetes mellitus (T2DM). Most of the cases of T1DM result from autoimmune destruction of the β -cells of the pancreas, which leads to insulin deficiency, termed type 1A diabetes mellitus. A minority of the T1DM patients have no evidence of autoimmunity but have permanent insulinopenia and are prone to ketoacidosis. This idiopathic form of diabetes mellitus is called type 1B diabetes mellitus. T2DM is characterized by insulin resistance.¹⁷ It often develops in adults and accounts for 90%-95% of the total diabetic population. Most patients with T2DM are obese, and the risk of developing T2DM increases with age, obesity, and lack of physical activity.¹⁵ T2DM has evolved as a rapidly increasing epidemic that parallels the increased prevalence of obesity across the globe.¹⁶

Diabetes mellitus increases the risk of cardiovascular disease by 2-3-fold in men and 5-fold in women compared to non-diabetic population.^{18,19} The cardiovascular disease that frequently occurs in diabetic patients includes coronary heart disease, hypertension, and DCM.^{20,21} DCM is characterized by left ventricular dysfunction that is independent of ischemic heart disease and hypertension.^{4,5} The main morphological and structural changes in the myocardium include local inflammation, myocardial fibrosis, steatosis, apoptosis, and ventricular hypertrophy.²² It is estimated that DCM affects approximately 12% of the diabetic patients, and almost 22% of the subjects over 64 years-old.¹⁰ It is difficult to prevent the progression of

DCM to overt heart failure.^{23,24} Therefore, there is an urgent need to search new agents to treat DCM more effectively.

ROS as Principal Mediators of DCM

ROS are generated continuously as natural byproducts of the normal metabolism of oxygen.²⁵ The common forms of ROS identified in the human heart include the superoxide anion ($O_2^{\bullet -}$), the hydroxyl radical ($OH^\bullet$), hydrogen peroxide (H_2O_2), singlet oxygen, carbon-centered radical, peroxynitrite ($ONOO^-$), nitric oxide ($NO^\bullet$), and nitrogen dioxide radical. Under physiological conditions, the generation of ROS in the heart is low, and they are eliminated efficiently by natural antioxidant defense systems, such as the superoxide dismutase and the glutathione cycle.

ROS are excessively produced in diabetic patients and in diabetic animals through multiple pathways, including mitochondrial dysfunction, uncoupled nitric oxide synthase, endoplasmic reticulum stress, and activation and up-regulation of ROS-producing enzymes, such as NAD(P)H oxidase, cyclooxygenase, xanthine oxidase, lipoxygenase, and cytochrome P450 (Figure 1). These ROS include the highly reactive $O_2^{\bullet -}$ and $OH^\bullet$.²⁶ Oxidative stress occurs when ROS production overwhelms the endogenous antioxidant ability to neutralize these highly reactive chemical compounds. The heart is highly vulnerable to oxidative stress compared with other organs and tissues due to its low basal levels of antioxidants, differences in mitogen-activated protein kinase family, and lower activity of conitase (a Krebs cycle enzyme).²⁷⁻²⁹

ROS overproduced in diabetes mellitus are a major causative factor for the development and progression of DCM.³⁰ ROS cause impairments in the structure and function of the heart by attacking, denaturing, and modifying

Figure 2. Pathological effects of overexpressed ROS in the diabetic heart. ROS overproduced in diabetic cardiomyocytes have autocrine and paracrine effects on the cardiomyocytes themselves and neighboring and remote cells. Within the cardiomyocytes, ROS are able to cause energy deficiency, contractile impairment, apoptosis, ferroptosis, inflammation, fibrosis, and hypertrophy through intracellular signaling pathways (p38-MAPK, PKC, and NOX) and mitochondrial mediators. ROS could also induce apoptosis, ferroptosis, inflammation, fibrosis, and hypertrophy in remote and neighboring (endothelial, vascular, and fibroblasts) cells.

functional molecules and by activating redox-sensitive transcription factors and signal transduction pathways (Figure 2).¹¹⁾ These events result in energy deficiency, contractile dysfunction, necrosis, apoptosis, ferroptosis, inflammation, fibrosis, and hypertrophy of cardiomyocytes. ROS produced in cardiomyocytes have paracrine effects on neighboring and remote vascular cells and fibroblasts, leading to apoptosis, ferroptosis, inflammation, fibrosis, and hypertrophy. *In vivo* studies support that ROS produced excessively in diabetes mellitus cause endothelial dysfunction, microangiopathies, and atherosclerosis in blood vessels of diabetic patients.³¹⁾

Critical Importance of NRF2 in Myocardial Defense Against Oxidative Damage

NRF2 is a basic leucine zipper transcription factor with a cap'n'collar structure.³²⁾ It is highly expressed in normal hearts.³³⁾ Its human sequence contains 605 amino acids, which are divided into seven domains called NRF2-ECH homology (Neh). Each of its seven domains fulfills distinct functions. The Neh1 domain contains a cap'n'collar-basic leucine zipper motif that allows NRF2 to heterodimerize with Maf proteins and bind with DNA. The Neh2 domain contains the Kelch-like ECH-associated protein 1 (Keap1)-binding site (DLG and ETGE motifs in the N-terminal Neh2 domain), which is necessary for its cytoplasmic retention and degradation. The Neh3 domain

is fundamental for NRF2 transcriptional activation through binding with chromo-ATPase/helicase DNA-binding protein 6. Neh4 and Neh5 provide interactions sites for the nuclear cofactors RAC3/AIB1/SRC-3 and CREB-binding protein, which enhances the NRF2/antioxidant response element (ARE) pathways, partially by promoting acetylation of NRF2. The Neh6 domain may contain a degron that is involved in the degradation of NRF2. The Neh7 domain interacts with retinoid X receptor- α , which is responsible for NRF2/ARE signaling inhibition.

The basal activity of NRF2 as well as the magnitude of its activation in response to stress is tightly controlled. Under normal homeostatic (basal) conditions, NRF2 is kept in the cytoplasm by Keap1 and cullin 3 (Cul3), which degrades NRF2 by ubiquitination.³⁴⁾ Human KEAP1 is a 69-kD protein that contains 27 cysteine residues. It is a substrate adaptor for Cul3, which contains E3 ubiquitin ligase activity. Cul3 ubiquitinates NRF2, while Keap1 is a substrate adaptor protein that facilitates the reaction. Once NRF2 is ubiquitinated, it is transported to the proteasome, where it is degraded and its components recycled. Under normal conditions, NRF2 has a half-life of only 20 minutes and is maintained at a low level due to proteasomal degradation. Oxidative stress or electrophilic stress disrupts critical cysteine residues in Keap1, which leads to the disruption of the Keap1-Cul3 ubiquitination system.³⁵⁾ When NRF2 is not ubiquitinated, it builds up in the cytoplasm and translocates into the nucleus.³⁶⁾ In the nucleus,

Figure 3. Schematic representation of NRF2 activation and antioxidant role in cardiomyocytes. Under basal conditions, NRF2 in the cytoplasm is constitutively bound to Keap1 and held in an inactive state. Keap1 functions to inhibit the NRF2 signaling pathway by promoting NRF2 ubiquitination through Cul3 and subsequent degradation of NRF2 by the proteasome. In responses to ROS, the NRF2-Keap1 complex is disrupted, and both the released and newly synthesized NRF2 translocates to the nucleus, where NRF2 binds to AREs in the promoter region of its target genes and promotes transcriptional activation of antioxidants and detoxifying enzymes.

NRF2 combines with one of the small Maf proteins (MAFF, MAFK, MAFK) and binds to AREs in the upstream promoter region of many antioxidant genes to stimulate transcription of antioxidant genes (Figure 2). It has been known that the activation of NRF2 results in the induction of many cytoprotective proteins, including NAD(P)H quinone oxidoreductase 1, glutamate-cysteine ligase, sulfiredoxin 1 and thioredoxin reductase 1, heme oxygenase-1, glutathione S-transferase family, UDP-glucuronosyltransferase family, and multidrug resistance-associated proteins.^{31,37)}

The expression of NRF2 in the heart is regulated by the gene *LAZ3* (*BCL-6*) and microRNA-21 in DCM.³⁸⁾ *LAZ3* encodes a sequence-specific transcriptional repressor which contains six zinc-finger motifs and shares amino-terminal homology with several transcription factors.³⁹⁾ The small noncoding RNA microRNA-21 is an important microRNA that is regulated in all types of diabetes mellitus and heart disease.⁴⁰⁻⁴³⁾ In the streptozotocin-induced cardiomyopathy of T1DM in mice, *LAZ3* was down-regulated and microRNA-21 was up-regulated.³⁸⁾ Overexpression of *LAZ3* decreased the expression of microRNA-21 and protected the heart against DCM, which was abrogated by the NRF2 small interfering RNA.³⁸⁾ Thus, it is likely that the regulatory effect of *LAZ3* on DCM is mediated by microRNA-21 and NRF2.

The NRF2/Keap1/ARE pathway is the major mechanism of myocardial defense against oxidative damage in diabetes mellitus and high glucose (Figure 3).⁴⁴⁾ This pathway regulates the expression of over 200 genes, many of which are related to reduction of oxidative stress and cell death. For example, the NRF2/Keap1/ARE signaling regulates direct antioxidant proteins, phase I and II electrophile detoxification enzymes, and free radical metabolism, inhibits inflammation, maintains glutathione homeostasis,

recognizes DNA damage, as well as regulates the expression of various growth factors and transcription factors. They have been shown to attenuate oxidative stress-induced myocardial injury and prevent the progression of DCM.^{45,46)}

As a key master switch controlling the expression of antioxidant and protective enzymes, NRF2 modification significantly impacts the cardiac and vascular phenotype. Genetic deletion of NRF2 in mice resulted in cardiac hypertrophy, left ventricular diastolic dysfunction, and decreased responses to β -adrenergic stimulation and ouabain.⁴⁷⁾ Left ventricular dysfunction in NRF2-null mice was associated with the down-regulation of the sarcoplasmic reticulum Ca^{2+} -ATPase in the myocardium.⁴⁷⁾ In addition, systemic blood pressure was decreased, and endothelial nitric oxide synthase was up-regulated in the aorta and heart of NRF2-null mice.⁴⁷⁾

Beneficial Effects of NRF2 Activators on DCM

The above results clearly indicate that oxidative stress is a key mechanism by which diabetes mellitus induces DCM. Hence, targeting oxidative stress-related processes in DCM could be a promising strategy for preventing the development of DCM. NRF2 and its downstream signaling pathways are key in preventing high glucose-induced oxidative damage in the cardiovascular system.⁴⁸⁻⁵¹⁾ Many natural and synthetic activators of Nrf-2 have been shown to possess promising therapeutic effects on DCM in animal models of DCM.^{5,52,53)} Although the data regarding the clinical trials of NRF2 activators on DCM are limited, NRF2 has been considered as a promising therapeutic target for DCM (Figure 4).⁵³⁾ In this section, we discuss several of the NRF2 activators that have a good potential, including sulforaphane (SFN), resveratrol

Figure 4. Schematic diagram illustrating the activation of NRF2 as a potential therapeutic target in diabetic cardiomyopathy. Diabetes mellitus elevates the production of ROS, leading to diabetic cardiomyopathy. NRF2 activators disrupt the NRF2-Keap1 complex, causing NRF2 release, or increase the expression of NRF2. In the nucleus, NRF2 promotes transcriptional activation of antioxidants and cardioprotective genes by binding to its target genes, leading to a decrease in the ROS and oxidative damage as well as to the amelioration of diabetic cardiomyopathy. Thus, NRF2 could be a therapeutic target in diabetic cardiomyopathy.

(RSV, 3,4,5-trihydroxystilbene), curcumin, dimethyl fumarate (DMF), rutin (3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside), and myricetin (Table).

SFN: SFN is a molecule within the isothiocyanate group of organosulfur compounds from cruciferous vegetables, such as broccoli, brussel sprouts, or cabbage. It has been chemically synthesized.⁵⁴ As a potent NRF2 activator, SFN has been extensively studied for its effects on diabetic complications.^{50,55-57} In the streptozotocin-induced mouse model of T1DM, SFN significantly up-regulated NRF2 and improved cardiac function.⁵⁵ The beneficial effects of SFN on diabetic mice are attributed to the reduction of oxidative stress-induced cardiac damage, inflammation, and fibrosis.⁵⁵ Similarly, in the mouse model of T2DM, SFN was able to activate NRF2 antioxidant signaling and prevent T2DM-induced lipotoxicity and cardiomyopathy.^{56,57} Moreover, SFN reduced fasting blood glucose and glycated hemoglobin in obese patients with T2DM.⁵⁸ Translation of SFN to the clinic has been achieved by administration of SFN-containing broccoli sprout powder to patients with T2DM.^{59,60}

RSV: RSV exists naturally in grapes, berries, nuts, and various other plants. It is a potent NRF2 activator and inhibits oxidative stress. RSV possesses multiple pharmacologic benefits, including anti-hyperglycemic, vasodilatory, anti-fibrotic, anti-inflammatory, and anti-apoptotic effects in animal models.⁶¹⁻⁶⁴ Recently, a large body of pre-clinical evidence has shown that RSV protected the heart against DCM.^{14,62,65-71} There are some clinical data regarding the favorable effects of RSV on DCM.^{72,73} The high safety profile of RSV coupled with its multidirectional effects has made it an attractive candidate to use in the

clinical trial of DCM.

Curcumin: Curcumin is a natural compound isolated from turmeric. It has been used for the treatment of obesity, metabolic syndrome, and prediabetes.⁷⁴⁻⁷⁶ In the streptozotocin-induced T1DM in rats, curcumin attenuated oxidative-induced cardiac damage, myocardial hypertrophy, and apoptosis, thereby ameliorating the function of the left ventricle.⁷⁷⁻⁷⁹ Curcumin activated the NRF2 system, repressed inflammation, and decreased the levels of fasting blood glucose and glycated hemoglobin in T2DM patients.⁷⁴⁻⁷⁶ The protective effect of curcumin on DCM is associated with increased heme oxygenase-1, catalase, superoxide dismutase, and glutathione and decreased expression of the NAD(P)H oxidase subunits p22 phox, p47 phox, p67 phox, and gp91 phox.^{77,78,80}

DMF: DMF is an electrophilic compound and is marketed under the name Tecfidera®. It stimulates the NRF2 transcriptional pathway to induce anti-oxidant and anti-inflammatory phase II enzymes to prevent chronic neurodegeneration.⁸¹ DMF is currently used as the first line of treatment in patients with relapsing multiple sclerosis. The monoester form of DMF, monomethyl fumarate, is its active metabolite. Recently, DMF was shown to improve cardiac function in a mouse model of T1DM.¹³ This favorable effect of DMF is attributed to the activation of the NRF2 signaling pathway, which results in the attenuation of oxidative stress, inflammation, fibrosis, and endothelial dysfunction.¹³ New formulations of DMF are being tested to improve the drug bioavailability and efficacy.⁸² These new formulations of DMF may have potential to use in the clinical trial of DCM.⁸³

Rutin: Rutin is a flavonol. It can be extracted from many nature sources, including buckwheat, oranges, grapes, lemons, limes, peaches, and berries. Rutin is a phytochemical with multiple pharmacological activities, including anti-diabetic, anti-oxidative, and free radical-scavenging bioactivities.⁸⁴ Many studies have shown that rutin alleviated DCM and improved cardiac function in animal models of both T1DM and T2DM.⁸⁵⁻⁹⁰ Mechanistically, the protective effects of rutin on DCM are associated with the reduction of oxidative stress, apoptosis, and inflammation.⁸⁵

Myricetin: Myricetin is a widely distributed flavonol compound found in many plants, including tea, berries, fruits, vegetables, wines, and medicinal herbs.⁹¹ This phenolic compound exhibits a wide range of activities including strong anti-oxidant, anticancer, antidiabetic, anti-inflammatory, antihypertensive, and immunomodulatory activities.⁹¹ Emerging studies indicate that myricetin alleviated cardiac hypertrophy, apoptosis, and interstitial fibrosis, leading to attenuation of DCM in the animal model of T1DM.⁹² The protective effects of myricetin on DCM are associated with the inhibition of IκBα/NFκB and enhancement of NRF2/heme oxygenase-1 and mitochondrial density.^{92,93}

Concerns about Facilitating Tumor Growth of NRF2 Activators

NRF2 is aberrantly accumulated in many types of cancers, including lung, breast, ovarian, head and neck,

Table. Beneficial Effects of NRF2 Activators on Diabetic Cardiomyopathy in Experimental Animals

Compounds	Animal models	Effects	Main mechanisms	References
Sulforaphane	T1MD mice	Ameliorates DCM Prevents diabetes-induced cardiac oxidative damage Attenuates inflammation and fibrosis	Up-regulates NRF2	50
Sulforaphane	T2MD mice	Ameliorates DCM Represses oxidative stress Attenuates inflammation and fibrosis	Up-regulates NRF2 Enhances NRF2 activity	51, 52
Resveratrol	T1MD rats	Ameliorates DCM Represses oxidative stress Reduces apoptosis	Activates NRF2	64
Resveratrol	T1MD mice	Ameliorates DCM Represses oxidative stress Attenuates fibrosis	Increases NRF2 expression	8
Curcumin	T1MD rats	Ameliorates DCM Represses oxidative stress Attenuates apoptosis, inflammation, and fibrosis	Increases Akt and GSK-3 β phosphorylation, inhibits protein kinase C-MAPK-pathway	72, 73
Dimethyl fumarate	T1MD mice	Ameliorates DCM Represses oxidative stress Attenuates inflammation and fibrosis	Activates NRF2	7
Rutin	T1MD rats	Ameliorates DCM Represses oxidative stress Attenuates inflammation and fibrosis		80, 83
Rutin	T2MD mice	Ameliorates DCM Represses oxidative stress Attenuates fibrosis Promotes angiogenesis		84

DCM indicates diabetic cardiomyopathy; GSK-3 β , glycogen synthase kinase-3 β ; MAPK, mitogen-activated protein kinase; NRF2: nuclear factor-erythroid 2 p45-related factor 2; T1DM, type 1 diabetes mellitus; and T2DM, type 2 diabetes mellitus.

and endometrial cancers in humans.^{94,95}) Persistent high expression of NRF2 in cancer tissues protected cancer cells from chemotherapeutic agents and facilitated cancer progression.⁹⁶) Overexpression of NRF2 is associated with a poor prognosis in cancer patients.⁹⁷) Moreover, *NRF2*-null mice are more prone to develop cancer in response to chemical and physical stimuli (nitrosamine, ultraviolet light, aflatoxin).⁹⁸) These facts suggest that NRF2 has a “dark side” related to its oncogenic activity when constitutively and highly overexpressed. Although a number of NRF2 activators have been evaluated for efficacy in humans (e.g., dithiolethiones, isothiocyanates, and triterpenoids), there is no evidence indicating direct genotoxicity and enhancing tumor growth of these agents to date.

Challenges of NRF2 Activators to Treat DCM

Diabetes mellitus and cancers are common diseases with a tremendous impact on health worldwide. Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for many forms of cancers.^{99,100}) Oxidative stress plays a fundamental role in the pathogenesis of both DCM and cancers. The activation of NRF2 signaling pathway may benefit cardiovascular and tumor tissues in diabetes with tumors. Although there is no evidence that NRF2 activators may increase cancer occurrence, chronic utilization of NRF2 activators in cancer patients may enhance tumor metastasis and worsen prognosis.¹⁰¹) Future research needs to examine the effects of new NRF2 activators on both diabetic hearts and tumor tissues simultaneously in animal models of DCM with a variety of cancers.

Another challenge of NRF2 activators to treat DCM is cytotoxicity due to off-target effects. There is mounting evidence that NRF2 can cross-talk with many intracellular signaling pathways that are important for cell survival.¹⁰²) Many NRF2 activators, such as SFN, dithiolethiones, and 1 [2-Cyano-3,12-dioxooleana-1,9 (11)-dien-28-oyl] imidazole, react with cysteines, leading to the modulation of multiple intracellular signaling pathways.¹⁰³) Bardoxolone methyl was withdrawn from a phase III clinical trial in end-stage renal disease patients with T2DM resulting from unspecified serious adverse effects and mortality in the treated patients.¹⁰⁴) The adverse events associated with bardoxolone are due to off-target events rather than the activation of the NRF2-Keap1 signaling pathway. The identification of the cocrystal structure of Keap1 in complex with the Neh2 domain of NRF2 will provide opportunities to design molecules that specifically and selectively interfere with the binding of Keap1 and NRF2.

Ferroptosis is a recently discovered form of cell death, which has immense implications for both health and disease.¹⁰⁵) It is a non-apoptotic regulated cell death caused by uncontrolled iron-dependent lipid peroxidation. Ferroptosis is distinct in its morphological, biochemical, and genetic profile from other cell death mechanisms.¹⁰⁶) Almost all genes thus far implicated in ferroptosis are transcriptionally regulated by NRF2, including the genes for glutathione regulation, NADPH regeneration, which is critical for Gpx4 activity, lipid peroxidation, and iron regulation.^{107,108}) Although NRF2 activators likely have an integral and pervasive impact on the manifestation of ferroptosis,^{107,108}) little is known regarding the role and importance of altered ferroptosis by NRF2 activators in the

pathogenesis and development of DCM.

Conclusion

In summary, oxidative stress plays a vital role in the pathogenesis of DCM. As the center of the body antioxidant system, the NRF2/Keap1/ARE pathway is of great value in the treatment of DCM. There is a growing body of convincing experimental evidence demonstrating that pharmacological activation of NRF2 is beneficial in counteracting many of the pathological processes that occur in DCM. Although there are some challenges of the utilization of NRF2 activators to improve DCM, targeting NRF2 signaling by pharmacological entities may provide a therapeutic option to ameliorate DCM.

Disclosure

Conflicts of interest: The authors declare no conflicts of interest.

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