EMERGING ROLE OF NRF2 AS A POTENTIAL THERAPEUTIC TARGET FOR CARDIOVASCULAR DISEASES

Pharmacology

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ABSTRACT

Nuclear factor erythroid 2-like 2 (Nrf2) is a transcription factor playing a big part in dynamic control of the antioxidant and cytoprotective gene system via activating the antioxidant response element (ARE) expression. Several Nrf2-targeted enzymes are essential for cardiovascular disease pathogenesis and are closely correlated with atherosclerosis, myocardial ischemia, diabetic cardiomyopathy, and congestive heart failure; moreover, they function as sensitive and precise markers to represent the ventricular function in heart failure patients. Activation of Nrf2 offers cardioprotection by synchronized up-regulation of the processes of antioxidative, anti-inflammatory, and autophagy. Thus, it may be worth examining the possible role of the Nrf2 signaling in cardioprotection. This review will encapsulate the present information about the structure, regulation, and participation of Nrf2 in various cardiovascular disorders and related complications like diabetic cardiomyopathy, hypertension, and obesity. A particular focus is put on Nrf2 inducers, which are potentially attractive therapeutic candidates for several cardiovascular disorders.

KEYWORDS

Nuclear factor erythroid 2-like 2, Antioxidant, Atherosclerosis, Diabetic Cardiomyopathy

INTRODUCTION

Cardiovascular disorders are the major reason for deaths globally, and the majority of people die of them every year than from any other cause. The mortality from cardiac diseases and cerebrovascular accidents will grow to 23.3 million by 2030. Roughly 1 to 2 % of the adult population in developed nations suffer from congestive heart failure, with the occurrence growing to near 10 % in older populations with average ages of 70+ (Nag & Ghosh, 2014). Atherosclerosis is the primary cause of nearly 2/3rd of heart failure cases with reduced ejection fraction (Herrington et al., 2016). The other reasons being high blood pressure, heart valve disorder, and non-ischaemic dilated cardiomyopathy. The instigators of diastolic dysfunction comprise chronic high blood pressure and left ventricular hypertrophy (Velagaleti & Vasan, 2007). Besides, in diabetics, the incidence and mortality of all cardiovascular disorders are two to eight folds more than non-diabetics (Martín-Timón, 2014). Grasping the molecular connection between diabetes and the development/progression of heart disorder is very multifaceted. Hyperglycemia triggered reactive oxygen species (ROS) has been accused of a probable molecular mechanism that triggers and progresses diabetic cardiomyopathy and related endothelial dysfunction (Volpe et al., 2018). The latter emerges early in atherosclerosis development, which is a self-reliant predictor of cardiovascular consequences.

Free radicals have arisen as vital mediators of various physiological and pathological processes. Reactive oxygen and nitrogen species function as signaling messengers for the mediation of various biological responses, comprising several cardiovascular disorders like congestive heart failure, atherosclerotic heart disease, and cardiac arrhythmias (J. Zhang et al., 2016). Whether these species exercised, actions are advantageous or damaging relies on the location, nature, and levels of their development and the antioxidant protection system activity of the organism (Lobo et al., 2010). Usually, overproduction of ROS is characterized by cardiovascular disorders, while the production of chief reactive nitrogen species, such as nitrates and peroxynitrite, may decrease or increase according to the type of cardiac injury (Pacher et al., 2007). ROS comprises superoxide ion (O_2^-), hydroxyl radical (OH) and hypochlorite (ClO^-), which weakens heart function and enhances the vulnerability to cardiac arrhythmia by

direct toxic action, leading to enhanced heart muscles necrosis and apoptosis (Moris et al., 2017). The ROS scavengers, phase 2 detoxification enzymes, and other related antioxidant proteins that comprise an ARE in their genetic transcription initiation regions are essential elements of the cellular antioxidant protection mechanisms. The strongly conserved transcription factor, Nrf2 or nuclear factor erythroid-derived 2-like 2, is a chief regulator of the AREs. Most of the Nrf2 targeted enzymes are critical for cardiovascular disorder pathogenesis and are frequently linked with heart failure; moreover, they act as specific markers to reveal the ventricular operation in heart failure patients (Q. M. Chen & Maltagliati, 2018).

The principal aim of this paper is to examine existing evidence for the cardioprotective role of Nrf2 and its regulated genes in the development and progression of cardiovascular disorders and related complications.

NRF2 STRUCTURE

Nrf2 is a transcriptional factor belonging to the cap'n'collar (CNC) subfamily of the basic leucine zipper region (bZIP) and comprises 605 amino acids in its human sequence, which is further divided into seven protein domains called Nrf2 ECH homology domains (Neh); Neh1 to Neh7 (Canning et al., 2015). ECH (erythroid cell-derived protein with CNC homology) is a CNC family that can bind with small musculoaponeurotic fibrosarcoma (sMAF) proteins to link with deoxyribonucleic acid (DNA) and control gene regulation (Katsuoka & Yamamoto, 2016). Neh1 comprises a CNC-bZIP region, which gives it the ability to heterodimerize with sMAF proteins and attachment with DNA. The Neh2 domain contains the binding site of kelch-like ECH-associated protein 1 (KEAP1), which attaches to peptide sequence stretches; DLG motif having weak interactions with KEAP1 and ETGE motif having relatively strong interaction. This binding is essential for its cytoplasmic preservation and cleavage (Tian et al., 2018). The Neh3 domain is central to transcriptional activation of Nrf2 by interacting with chromodomain helicase DNA-binding protein 6 (CHD6). The domain has a potential role in transactivation of the nrf2 target genes (Nioi et al., 2005). Neh4 and Neh5 provide an interaction site for nuclear cofactor receptor-associated coactivator 3 (RAC-3) or steroid receptor coactivator 3 (SRC-3) and cAMP-response element-binding protein (CREBBP) that increases the Nrf2

activation pathways, moderately via the addition of acetyl group on Nrf2. This interaction increased the gene transcription rate. Also, Nrf2 has a redox-sensitive nuclear translocation signal inside the Neh5 domain, making Nrf2 capable of controlling its cellular position (Satta et al., 2017). The serine-abundant Neh6 domain has two peptide motifs (DSGIS and DSAPGS) concerned with the Nrf2's negative regulation. These domains are identified by β -transducin repeat-containing protein (β TRCP). Glycogen synthase kinase 3's (GSK-3) addition of phosphate group to serine residues in the DSGIS region allows interaction with BTRCP, which acts as a substrate receptor for S-phase kinase-associated protein 1–Cullin 1–Ring box protein 1 (Skp1–Cul1–Rbx1) complex, causing KEAP1-independent degradation (Chowdhry et al., 2013). Neh7 domain binds with the retinoid X alpha-receptor (RXR α), which is accountable for signaling inhibition of Nrf2/ARE (H. Wang et al., 2013).

KEAP1 is a 69 kD protein, with 27 residues of cysteine. It is a cullin 3 (Cul3) Substrate Adapter containing E3 ubiquitin ligase (Magesh et al., 2012). KEAP1 consists of five domains; an amino-terminus or N terminal region, a Broad-Complex, Tramtrack, and Bric-à-brac (BTB) domain having Cysteine-151 residue, an intervening region (IVR) domain comprising two essential Cysteine-273 and Cysteine-288 residues having a role in stress sensing, a double glycine repeat (DGR) or Kelch domain having six repeats with an end carboxyl-terminus or C-terminal region. The BTB domain homodimerizes with Cul3, creating an inhibitory Nrf2 complex. Cysteine-151 residue plays a vital role in activating Nrf2 activation under oxidative stress. Besides, the IVR domain is extremely oxidation sensitive and encompasses three significant cysteine residues; Cysteine-273, Cysteine-288, and Cysteine-297, which control the stimulation and repression of Nrf2 (Kansanen et al., 2003).

Figure 1: Domain structure of Nrf2 (Canning et al., 2015).

NRF2 ACTIVATION AND REGULATION

In physiological settings, Nrf2 is isolated in the cytoplasmic region when there is an equilibrium between oxidants and the sufficient action of antioxidant proteins. Such sequestration takes place adjoining to the cellular network of cytoskeleton through the interaction between Nrf2, Keap-1, and Cul3, the latter being an integral part of E3 ligase family protein (Kobayashi et al., 2004). KEAP1 functions as an adapter biomolecule for CUL-E3 ligase and regulates the nrf2 ubiquitination by Cul3 and the consequent degradation by the proteasome Cul3-Ribokinase1 complex (Sima et al., 2009). Consequently, Nrf2 has a brief half-life of just 20 minutes under typical physiological oxidative conditions (Q. Ma, 2013). The breakdown and ubiquitination are under the control of the initiation signal triggered by the development of the Nrf2-Keap-1-Cul3 complex, preserving the basal levels of Nrf2 and the genes mediated by it (Furukawa et al., 2004). It is unknown if the Nrf2 protein detaches from KEAP1 or whether the Cysteine-151 alteration simply prevents the subsequent processing of Nrf2 (Dayalan Naidu et al., 2018). The newly formed Nrf2, or protein detached from KEAP1, is then moved freely to the nucleus.

Furthermore, p21, p62, and Wilms tumor gene located on the X chromosome (WTX) also enhance Nrf2 activation by KEAP1 sequestration or attachment to Nrf2 to inhibit KEAP1 association (Camp et al., 2012). Of particular relevance to cardiovascular disorders, laminar shear stress induces endothelial cell stimulation of Nrf2 (Hosoya et al., 2005) via lipid peroxide and prostaglandin *15d-PGJ2*, increased by phosphatidylinositol 3-kinase/Protein kinase B (PI3K/PKB) pathway signaling, but is unexpectedly unaffected by endothelial nitric oxide synthase (eNOS) activity (Ramprasath et al., 2015). Moreover, the nuclear localization of Nrf2 is enhanced by laminar shear stress via a mechanism dependent on KLF2 (Hosoya et al., 2005). At the same time, phosphoinositide 3-kinase (PI3K), protein kinase C, c-Jun N-terminal kinase (JNK), activate Nrf2 by its phosphorylation, while GSK3 β is a unique negative regulator for Nrf2 [29]. GSK3 β initiates phosphoserine formation in the Neh6 domain while independently facilitating its breakdown concerning the KEAP1 pathway (Rojo de la Vega et al., 2018). At the same time, GSK-3 β can facilitate the nuclear transport of Nrf2 by triggering the phosphate group addition to Tyrosine-568 in Nrf2 via Fyn kinase, resulting in the inactivation of nuclear Nrf2 (Hosoya et al., 2005). Nrf2 activation in endothelial cells and immune-responsive monocytes is enhanced by the tumor necrosis factor- α (TNF- α) (Shanmugam et al., 2016).

After entering the nucleus, Nrf2 heterodimerizes with transcription factors, such as c-Jun, sMaf, which enables the entire basic zipper formation, and attachment to the promoter region of ARE to induce gene transcription (Wasserman & Fahl, 1997). This leads to an organized expression and activation of antiapoptotic, metabolic, and anti-oxidants proteins. The major antioxidant proteins mediated by Nrf2 are heme oxygenase 1 (*HMOX1*), Glutamate-Cysteine ligase modifier (*GCLM*), Protease-Activated Receptor 4 (PAR4) (Rwibasira Rudinga et al., 2018), glutathione peroxidase 1 (GPx-1) (Banning et al., 2005), catalase (CAT) (Dong et al., 2008), peroxiredoxin I (Prx I) (Kim et al., 2007), and superoxide dismutase (SOD) (Miller et al., 2012).

MicroRNAs (MiRNA) are regulatory elements that utilize co-transcriptional modifications or translational repressions to refine protein development (Jiang & Yan, 2016). Nrf2 activity is also controlled through miRNAs at the level of co-transcription (Shah et al., 2013). The imposed expression of human MiRNA precursors such as MiRNA144, MiRNA153, MiRNA27a and MiRNA142-5p impacts the translocation of Nrf2 and rate of transcription via suppressing KEAP1-independently the Nrf2's three prime untranslated region and internal mRNA, and either of these independently or as a group may impact Nrf2, thereby sparking or having a say on specific disease outcomes (Narasimhan et al., 2012). The presence of complementary base pairs in MiRNA495 and Nrf2 suggests the presence of their possible binding sites and interplay between them, and denote that MiRNA495 can negatively regulate Nrf2 (Geng et al., 2018). Apart from MiRNAs, long noncoding RNAs (long ncRNAs), that can transcripts in lengths more than 200 nucleotides (Zampetaki et al., 2018) are also critical functional and regulatory factors in the pathogenesis and constant progression of disorders (Geng et al., 2018). Long ncRNA *NEAT2* (nuclear-enriched abundant transcript 2), also known as metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), is known to cooperate Nrf2 and suppress gene expressions that are guided as opposed to oxidative stress by Nrf2/ARE. The expression of Nrf2 and its related downstream genes rises in MALAT1-deficient mice, and the development of ROS also declines (J. Chen et al., 2018). However, another experimental study demonstrated the conflicting result that MALAT1 could assist the expression of Nrf2 by negative regulation of KEAP1, resulting in the suppression of oxidative stress, impairment of DNA structure, and lipid peroxidation (Fan et al., 2018). We assume this discrepancy might be associated with the variations in the experimental circumstances and disease models.

Nrf2 function is also dependent on epigenetic processes, such as the addition of a methyl group to DNA promoters, and alternations of histones (Huang et al., 2015). In the vertebrates, heritable methylation occurs in the cytosine-guanine (CG) dinucleotides sites of DNA, only at the fifth position of the nucleotide cytosine chain (M. Zhang et al., 2019). CG islands were noted to take part in epigenetic covalent modification of Nrf2 in the promoters of Nrf2 (Yu et al., 2010). Such Epigenetic modification mechanisms lead to reduced Nrf2 expression, as the methylation blocks the transcription of the antioxidant genes targeted by Nrf2 (Su et al., 2014). Sulforaphane improves the Nrf2 expression via the removal of methyl groups from CG islands by

epigenetic regulation, consequently initiating its downstream oxidative stress opposing pathway (C. Zhang et al., 2013). The operation of Nrf2 can be hindered by avoiding its acetylation (Tebay et al., 2015). It has been verified that CREBBP can cause acetylation of Nrf2 at the Lysine residues in the Neh1 domain, and this modification increases the Nrf2's capacity to bind with DNA and its overall functioning (Z. Sun et al., 2009). Finally, K(lysine) acetyltransferase 8 (KAT8), a histone acetyltransferase, can cause acetylation of Nrf2, which induces withholding of Nrf2 in the nucleus and defend against oxidative stress (Z. Chen et al., 2014).

NRF2 AND ITS MITOCHONDRIAL FUNCTION IN CARDIOVASCULAR DISEASES

Stroke, atherosclerotic heart disease, myocardial ischemia-reperfusion injury, and congestive heart failure are the major causes of cardiovascular illness and mortality. Many risk factors are implicated in cardiovascular disorders, where ROS is a key mediator and is upregulated due to several risk elements like type 2 diabetes, and inflammation (Chang, 2012). Oxidative stress can lead to endothelial cells death and stimulate the transcription protein nuclear factor kappa-B (NF- κ B), enhancing adhesion molecules and inflammatory cytokines to increase monocyte adhesion (Postea et al., 2006). Oxidative stress entails mitochondrial dysfunction, which is associated with bioenergetic deficiencies and modified mitochondrial dynamics. This causes defects in the transcriptional process and injury to the cells. During myocardial ischemia-reperfusion injury, extreme oxidative stress and calcium imbalance results in irregular permeation, swelling of mitochondria, and defects in mitochondrial permeability transfer pore, resulting in impairment of electron transfer chain (Halestrap, 2004). Blocking the movement of mitochondrial electrons in complex III in type 2 diabetes results in the discharge of electrons, reducing oxygen to O⁻, and increasing the formation of intracellular ROS (Bleier & Drose, 2013). Oxidative stress can also stimulate membrane oxidases with a corresponding enhancement in N,N-Dimethylarginine concentrations contesting for L-arginine carriers, and active sites on endothelial nitric oxide synthase 3 (Wilcox, 2012).

Nrf2 controls mitochondrial respiration chain function, with pharmacological stimulation of Nrf2 defensive mechanism against cytotoxicity, and likely preserving mitochondrial equilibrium through the suppression of RAC-beta serine/threonine-protein kinase (Akt2) signaling (S. Wang et al., 2017). Nrf2 is directly involved in the expression and development of antioxidant mitochondrial proteins; it stimulates the expression of GPx-5, GPx-3 (Singh et al., 2006), and thioredoxin reductase 2 (Locy et al., 2012), believed to be Nrf2-dependent, causing mitochondrial defense against oxidative injury. Piantadosi and colleagues observed that HMOX1 involvement in the mouse's cardiac function activates the cycle of mitochondrial biogenesis controlled by Nrf2 and decides the central feature of the defense mechanism for HMOX1 (MacGarvey et al., 2012).

Uncoupling protein 3 (UCP3), an inner mitochondrial membrane protein (Boss et al., 1997), controls the efficacy of energy metabolism by facilitating the movement of protons and thus decreasing the formation of O⁻ (López-Bernardo et al., 2015). Nrf2 is engaged in upregulating the UCP3 expression, facilitating the survival of cells under conditions of oxidative stress. Upon ischemia-reperfusion injury, the tissue causes the opening of mitochondrial permeability transition pores and succeeding apoptosis. Kim and colleagues noted that the mitochondrial ATP dependent potassium channels tend to interact with mitochondrial ROS. Therefore, it is speculated that organosulfur sulforaphane's protective effects against myocardial ischemic reperfusion injury may be controlled by the antioxidant pathway and the mitochondrial ATP dependent potassium channels.

ROLE NRF2 IN CARDIOVASCULAR CONDITIONS

Atherosclerosis

Throughout the atherogenesis cycle, lipids keep on loading in the arterial intima causing many modifications in the arterial wall, such as the formation of fatty streaks, poorly functioning endothelial cells, enhanced recruitment, and stimulation of immune cells and the vascular smooth muscle cells proliferation (Raggi et al., 2018). The latter results in continuous cytokine and oxygen radicals' production that play a role in further atherosclerotic lesion development (Koelwyn et al., 2018). Although ROS are essential for signaling molecules that control vascular homeostasis, the disproportionate ROS, which is enhanced by several risk factors linked with atherosclerosis, advances

the endothelial dysfunction and reduces the bioavailability of nitric oxide. Oxidative stress causes low-density lipoprotein (LDL) oxidation to synthesize ox-LDL, which leads to an augmentation of oxidative stress and the development of foam cells in the walls of arterial blood vessels, exacerbating the development of atherosclerotic plaque (Koelwyn et al., 2018). Aggregation of lipids in the tunica intima is linked to oxidative stress and inflammation, resulting in dysfunction of endothelial (YILDIZ, 2007). By stimulating the expression of adhesion molecules and chemokines, inflammatory signaling molecules lead to monocyte recruitment into the tunica intima. Nrf2 stimulation decreases the response of endothelial cells to inflammation. Thus, the expression of antioxidant genes mediated by Nrf2 that can be instrumental in atheroprotective function in endothelial cells.

In line with this theory, the Nrf2 controlled gene, HMOX1, showed substantial cytoprotective and anti-inflammatory actions leading to decreased atherosclerosis in various mouse models (Lazaro et al., 2018), probably by generating low carbon monoxide (CO) concentrations. High cholesterol-fed mice, lacking in HMOX1, displayed increased atherosclerosis progression relative to normal mice. Enhanced neointimal formation and eventually increased cell atrophy shown by smooth muscle cells in HMOX1 deficient mice is due to increased exposure to oxidant stress (Sussan et al., 2008). HMOX1 expression in phagocytic macrophages display a protective function in atherosclerosis (Lazaro et al., 2018) with macrophages in the HMOX1^{-/-} showing increased production of oxygen radicals, enhanced inflammatory cytokine release, and increased development of foam cells when administered with ox-LDL, partially because of enhanced expression of scavenger receptor A (SR-A).

Straight parts of the blood vessels that are subjected to regular laminar flow of blood are somewhat secured from atherosclerosis by organized gene expression regulation, primarily regulated by Krüppel-like factor 2/Krüppel-like factor 4 (KLF2/KLF4) and Nrf2 stimulation (Nayak et al., 2011), (Nakajima & Mochizuki, 2017). Endothelial cells are subjected to turbulent flow; on the other hand, they implement a phenotype that increases the endothelial dysfunction and enhances permeability. Increased HMOX1 expression decreases the ox-LDL led stimulation and expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) (H. Zhang et al., 2013). Also, the Nrf2/ARE signaling reduces the expression of TNF- α -stimulated oxidative stress-sensitive inflammatory genes such as VCAM-1 and monocyte chemoattractant protein (MCP-1) (X.-L. Chen et al., 2004). These findings suggest that activation of Nrf2 is atheroprotective because of its antioxidant and anti-inflammatory activities, which reduce the harmful effects exerted on endothelial cells by *hypercholesterolemic* and inflammatory reactions. However, further studies are required to have more understanding of the role of Nrf2 in the various stages of atherosclerotic plaque progression.

Hypertension

The physiopathology of hypertension includes several factors: a more activated renin-angiotensin-aldosterone system (RAAS) and stimulated sympathetic nervous system [59]. Both the processes mediate the pressure of blood, sodium intake, potassium removal from the body, and vasoconstriction (Muñoz-Durango et al., 2016). The fundamental cause of severe hypertension and cardiovascular mortality is impaired functioning and activation of RAAS. The upregulation of RAAS enhances the expression and actions of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and generates free radicals that possibly regulates some of the effects of hypertension induced by it (Nguyen Dinh Cat et al., 2013). Oxidative stress due to excess free radicals stimulates a wide variety of hypertrophy-inducing protein kinases and various transcription factors in the cardiovascular system, and it has been reported as one of the significant pivotal factors in inducing cardiac hypertrophy (Jia et al., 2018). Hypertension has been proposed as one of the significant factors behind the misregulation of Nrf2 and not conversely, increased oxidative stress and dysfunction in vessels in a hypertensive rat model (C. Wang et al., 2018). Fibrosis facilitates the production of cardiac dysfunction in hypertrophied heart muscle cells (Wakui et al., 2013). Nrf2 activation and subsequent expression of its regulated genes present a new mechanism for shielding the heart from pathological ventricular remodeling via reduction of oxidative stress (Shanmugam et al., 2019), (Z. Lu et al., 2008).

Compared to wild mice, Nrf2-knockout mice were found to have

cardiac hypertrophy, severe fibrosis of heart muscles, apoptosis, evident heart failure, and enhanced morbidity, which correlated with high concentrations of 4-Hydroxynonenal (4-HNE) and 8-Oxo-2'-deoxyguanosine in the myocardium expression and total suppression of many antioxidant genes (X. Li et al., 2018). Nrf2 overexpression significantly reduced the progression of hypertrophic factor-stimulated free radicals in both heart muscles and fibroblasts, while Nrf2 knockdown demonstrated the opposite actions in both cells (J. Li et al., 2009). Hence, Nrf2 plays a vital regulator in sustaining the typical cardiac structure and functioning in an exceptionally stressed heart.

HMOX1 also defends against the heart hypertrophy (Araujo et al., 2012). Hu et al., for instance, stated that HMOX1 prevented angiotensin II stimulated myocardium hypertrophy in both in-vitro and in-vivo conditions (Hu et al., 2004). Ndisang and Jadhav, further demonstrated that increased expression of HMOX1 reduced hypertrophy in left ventricles in spontaneously hypertensive rats, followed by reduced remodeling of the extracellular matrix. HMOX1, when suppressed by chromium (III) mesoporphyrin aggravated myocardium fibrosis (Ndisang & Jadhav, 2009).

SOD activity in heart muscles was reduced in transverse aortic constriction induced left ventricular remodeling (Hikoso et al., 2009). Furthermore, Angiotensin II increased collagen production and deposition and meanwhile suppressed SOD1 and SOD2 functioning in fibroblasts in hypertensive rat's hearts. Decreased expression of SOD2 led to enhanced oxidative stress in the heart and produced maladaptive cardiac hypertrophy (Kang et al., 2018). SOD3 deficiency intensified oxidative stress, heart failure, fibrotic processes, and hypertrophy, which were triggered by transverse aortic constriction (Z. Lu et al., 2008). These results show that activation of Nrf2 and its antioxidant downstream genes offer a novel mechanism to protect the heart muscles against excess pressure-induced cardiac hypertrophy, heart failure, cardiac fibrosis, and apoptosis.

Myocardial Ischemia

The advancement of coronary angioplasty and surgical revascularization has provided significant benefits for acute myocardial infarction patients. Increased heart injury is triggered by ischemic reperfusion during revascularization (Frank et al., 2012). Oxygen free radicals may be created by the myocardium itself or by infiltrating inflammatory cells soon after the blood flow is re-established (Braunersreuther & Jaquet, 2012). Oxidative stress can then cause cellular damage via a variety of pathways, including direct injury to cell membranes and proteins or secondary injury via proapoptotic pathway stimulation (Braunersreuther & Jaquet, 2012). This damage can cause more cardiac remodeling, causing advanced heart chamber dilation, thinned out the ventricular wall and in due course heart failure (Y. Sun, 2008). Nrf2 and its regulated antioxidant target genes have been demonstrated to play a defensive function in injury concerned with cardiac ischemia (Y. Shen et al., 2019).

Few antioxidants, via the Nrf2 pathway, protect the heart from cardiac injury caused by ischemia. For instance, -lipoic acid and prostaglandin D2 (PDG2) considerably enhanced Nrf2 translocation to the nucleus, and the activation of its downstream genes decreased the release of lactate dehydrogenase (LDH) and creatine phosphokinase, prevented myocardial infarction, reduced cell death of cardiomyocytes and moderately conserved cardiac function; and this action was to some extent reliant on PI3K/PKB signaling pathway (Deng et al., 2013).

Expression of HMOX1 in human heart failure and animal models of acute right ventricular failure can be documented by previous studies (Raju et al., 1999). HMOX1 expression in non-ischemic heart muscles was enhanced four weeks after the coronary artery was ligated, enhanced post-ischemic survival rates, reduced enlargement of heart cells, and interstitial thickening oxidative stress, and cell death were all revealed by cardiomyocyte-specific HMOX1 transgenic mice (G. Wang et al., 2010).

Besides, it has been noticed that GPx knockout mice are more vulnerable to myocardial infarct reperfusion trauma (Lim et al., 2009). GPx overexpression also mitigated post-myocardial infarction cardiac failure and heart remodeling by reducing myocyte hypertrophy, cell death, and interstitial thickening in the non-infarcted left ventricle, which may be linked to GPx maintaining complex functioning in the electron transport chain (Ribas et al., 2014). Upregulation of Nrf2 and its downstream antioxidant genes prevented myocardial ischemia

caused left ventricular remodeling and heart failure; therefore, heart injury treatment therapies intended to hinder oxidative stress may be helpful.

Obesity

Enhanced adipocyte's oxygen free radical production, which, as a consequence, increases the expression and production of inflammatory adipocytokines, has remarkable implications for energy homeostasis and vascular operation regulation. The risk of cardiovascular disorder is typical with this combination (Ha & Bauer, 2018).

New substantial data suggest that Nrf2 is concerned with regulating the metabolism of energy and maybe a potential therapeutic target for obesity. Numerous investigation methods such as Nrf2 gene deletion, its pharmacological activation, and overexpression have been done to understand the fundamental mechanism of the Nrf2 gene role in obesity. The ester epigallocatechin gallate stimulated activation of Nrf2 in hepatocytes and obese mice's adipose tissue perks up lipidemic regulation, reduces the development of oxidative free radicals, and decreases body fat reserves and glucose levels (Han et al., 2017). Intriguingly, the KEAP1 gene knockout mice display standard features, such as reduction of high lipid diet caused obesity and reduced lipid and bad cholesterol deposition in the liver (Slocum et al., 2016). Notably, a better metabolic profile is closely related to improved heart function (Tune et al., 2017). Likewise, a high-lipid diet caused oxidative stress, thickening of tissue, fibrosis, hypertrophy, and cardiac remodeling. These advantages are closely related to enhanced expression of Nrf2 and reduced production of ROS (Xiang et al., 2020).

The mutation of the Nrf2 gene is anticipated to enhance the generation of oxygen free radicals and intensify the obesity phenotypes. Nrf2 knockout mice have enhanced oxidative stress, free fatty acids build up and deposition in the liver, and boosted expression of genes linked with the production of lipids and cholesterol (Tanaka et al., 2008). In line with these results, it was demonstrated that mice's obesity facilitates vascular oxidative stress by enhancing the expressions of Nrf2 and KEAP1 downregulating proteins (da Costa et al., 2019).

Nrf2 was also investigated for its role in the operation of adipose tissue actions and metabolic syndrome. The function of Nrf2 in the progress of obesity and related metabolic diseases was found by encompassing the Nrf2-knockout animal model of leptin-deficient (ob/ob) mice. (Xue et al., 2013). In these obese mice, the deletion of Nrf2 in adipocytes decreases the mass of white fat. Exacerbated insulin resistance, diabetes, and elevated triglycerides level are some examples of extreme metabolic syndrome that can be seen with the deletion of the Nrf2 gene. Nevertheless, it also led to extreme metabolic syndrome with exacerbated insulin resistance, diabetes, and elevated triglycerides. These results endorse Nrf2's function in controlling the production and regulation of adipocytes, insulin sensitivity, and lipid homeostasis.

ROLE OF NRF2 IN DIABETIC CARDIOMYOPATHY AND RELATED COMPLICATIONS

There is ample proof that oxidative damage done by oxygen free radicals leads to the initiation and complications of *type 2 diabetes* (David et al., 2017; Oberley, 1988). However, it has only lately begun to elucidate the role of the *Nrf2-KEAP1-ARE* signaling pathway in the physiopathology of diabetes and the broad extent of its complications, such as diabetic kidney disease and defected wound healing of cutaneous tissues. As mentioned in the recent *nrf2* analysis, this pathway is also linked to diabetic damage to the heart (Y. Li et al., 2017). Animal studies and outcomes of clinical trials offer encouraging observations indicating that stimulating this signaling pathway can postpone or even overturn diabetes-associated dysfunctions (de Haan, 2011).

Experimental proofs indicate the link between diabetes and a decreased antioxidant defense mechanism and subsequent increased oxidative stress. Excess free radical production allows diabetic repercussions, such as cardiomyopathy, to develop; whereas, antioxidants can suppress or cure the same (Hill, 2008). Also, Nrf2 and its marked genes are downregulated in heart muscles in diabetic mice (Uruno et al., 2013), which might be due to extracellular signal-regulated kinases 1/2 activity (ERK1/2) (Cai et al., 2005). Myocardial severe damage, which is led by increased oxidative stress, is caused by diabetes-induced loss of Nrf2 activity (Q. Liu et al., 2014). Therefore, activation and increased expression of endogenous antioxidant

proteins have been suggested as an attractive technique for preventing diabetic complications (Pitocco et al., 2013). This pathological cycle might be prevented or inhibited by Nrf2 and its marked genes. Tan et al. also found that Nrf2 overexpression was enhanced marginally in mice's hearts with 60 days hyperglycemia but reduced significantly in mice with 150 days hyperglycemia, which indicates that Nrf2 was adjustably overexpressed at the initial phase of diabetes to mitigate diabetic damages; nevertheless, at the latter phase, the heart antioxidant role was so severely damaged that the cardiac Nrf2 expression reduced (Y. Tan et al., 2011).

Diabetics with longer HMOX1 gene promoter repetitions were more prone to oxidative stress and enhanced coronary artery disease vulnerability (Y.-H. Chen et al., 2002). In a streptozotocin mediated diabetes models, increased expression of HMOX1 reduced left ventricular dysfunction, disordered myofibrils structural composition, resulted in physiological oxidative stress, cell death, and autophagy (Y.-H. Chen et al., 2002). Besides, HMOX1 deficiency substantially enhanced the size of the infarcted region in non-diabetic mice and worsened myocardial infarction complications in diabetic mice (X. Liu et al., 2005). Besides a more prominent infarcted region, deaths were twice as more in diabetic HMOX1-knockout mice as in wild mice following ischemia-reperfusion injury, and more than 50 % of diabetic HMOX1-knockout mice endured the ischemia-reperfusion injury-induced left ventricular thrombi (X. Liu et al., 2005). Myocardial SOD function and glutathione level in the hearts of diabetic rats were also enhanced considerably (Z. Xia et al., 2006). Diabetes stimulated cardiac structural modifications were preserved by overexpression of SOD2, and the defected contractility in cardiomyocytes was fully stabilized (L. Shen et al., 2006). Besides, GPx overexpression has prevented the development of diabetes-related left ventricular remodeling and diastolic dysfunction (Matsushima et al., 2006).

Diabetes induced endothelial dysfunction is related to oxidative stress, increased blood vessels contractility, and inflammation (Avogaro et al., 2011). Recent experimental studies have shown that bardoxolone methyl analog, dihydro-CDDO-trifluoroethylamide, at small doses, decreases atherosclerosis progression in apolipoprotein E knockout mice and plays a defensive role, both in vivo and in vitro against endothelial dysfunction caused due to type 2 diabetes (S. M. Tan et al., 2014). Since endothelial dysfunction, the first step in the initiation of diabetic complications in vessels is led by oxidative stress and pro-inflammatory actions, the atheroprotective effects of dihydro-CDDO-trifluoroethylamide could be due to recovering endothelial function. In line with these findings, enhanced expression of Nrf2 action, for example, by bardoxolone methyl (RTA-402) or the isothiocyanate sulforaphane, reduces the increased vascular contraction (Sharma et al., 2017) and mitigates decreased vasodilatory action in diabetic mice (Chin et al., 2014).

One suggested endothelial functioning improvement mechanism after the activation of Nrf2 is the enhanced formation and expression of a big potassium channel subunit $\beta 1$ (BK- $\beta 1$), and its suppressed degradation (T. Lu et al., 2017), a process generally sped up by oxidative stress due to type 2 diabetes (J. Liu et al., 2016). Other reasons include decreased oxidative stress in vessels, and enhanced nitric oxide bioavailability (Pereira et al., 2017). Beyond this immediate homeostatic response, over the long-term implications of Nrf2 activity have also been explained as vital causes of diabetes-induced vascular complications. Correspondingly, the literature identifies functional interactions between Nrf2 and signaling pathways such as the NF- κ B, tumor protein 53, ERK5, mammalian target of rapamycin 46, heat stress genes, and activator protein-1 (AP-1) (Hwang et al., 2017). This means that, ahead of its instant homeostatic properties and cytoprotective actions, Nrf2 controls other cellular functions and affects systemic processes such as inflammation, cellular proliferation, cell death, cell differentiation, and tissue regeneration. Indeed, in the diabetic cardiomyopathy model, reduced Nrf2 expression is observed, along with a reduction in downstream expression of Nrf2 regulated antioxidant proteins and enhanced oxidative stress (Yonggang Wang et al., 2014).

Nrf2-knockout mice display modifications in the structure and abnormal functionality under conditions of oxidative stress, and Nrf2-knockout mice's heart muscle cells display considerably enhanced apoptosis after incubation with very high glucose concentrations (He et al., 2009). The proteasome suppressor Z-L-Leu-D-Leu-L-Leu-al (MG132) was shown to reduce left ventricular hypertrophy by

decreasing inflammatory processes and reducing the possibility of cardiomyopathy (Lee et al., 2016). Moreover, Nrf2 stimulation by sulforaphane lowered heart mass and reduced type 2 diabetes caused atrial natriuretic peptide's expression, which is considered to be related to the induction of diabetic cardiomyopathy in a diabetes mouse model (Xin et al., 2018).

Improving the expression of endogenous Nrf2 and the corresponding antioxidant pathways in the cardiac tissues is, therefore, a possible strategy to avoid diabetic cardiomyopathy and endothelial dysfunction.

Figure 2. Representation of factors leading to oxidative stress and dysregulated Nrf2 expression caused Diabetic cardiomyopathy (Matzinger et al., 2018).

NRF2 INDUCERS

Cardiovascular disorders have a time reliant evolution. It opens the windows of chance for medications encompassing synthetic pharmacological and natural therapeutic drugs. Considering the ample proof for a protective function of Nrf2, one would assume that compounds that induce Nrf2 are attractive candidates for several cardiovascular disorders.

Most activators of Nrf2 are natural products and phytoconstituents extracted from plants. Examples of such activators are sulforaphane, curcuminoid curcumin, stilbenoid resveratrol, chalcones-butein, phloretin, and organosulfur compounds found in garlic (Jadeja et al., 2016), (Dinkova-Kostova et al., 2017). Many synthetic Nrf2 activators, such as MG132, 4-HNE, α -lipoic acid, hydrogen sulfate, RTA-402, and 17 β -estradiol (E2) have also been synthesized (Cui et al., 2013), (D. Xia et al., 2019), (Zhou et al., 2014), (Cuadrado et al., 2019). They exercise their actions by triggering a defensive mechanism controlled by Nrf2 and stimulating phase II detoxification proteins, enzymes, antioxidants, and carriers that safeguard cells from elevated oxidative stress (Cuadrado et al., 2019).

Natural

Sulforaphane, an isothiocyanate found in Brassicaceae family vegetables like cauliflower, and broccoli is a comprehensively reviewed natural product that targets the Nrf2-KEAP1 signaling transduction pathway (Sturm & Wagner, 2017). Sulforaphane treatment reduced the size of the infarct, suppressed an elevation in the left ventricular end-diastolic pressure, and bettered the coronary blood flow in mice after myocardial infarction (Piao et al., 2010). The expression HMOX-1 and SOD can somewhat mediate this defensive action (Piao et al., 2010). Sulforaphane also improved the expression of antioxidant enzymes and induced cytoprotective proteins, such as GCLM, and increased expression is primarily regulated by Nrf2 (Y. Liu et al., 2019).

Curcumin is a well-documented natural drug, capable of stimulating Nrf2 (BALOGUN et al., 2003). Curcumin was used in rats to reduce cardiomyopathy caused by doxorubicin (Venkatesan, 1998). Curcumin pre-treatment in this experimental study annulled the elevation in lipid peroxidation and CAT levels and reduced the doxorubicin caused high glutathione level and GPx activity in rat heart tissues (Venkatesan, 1998).

The treatment of cardiac stem cells in a rat left anterior descending occlusion model with the natural phenol resveratrol; it was observed that that resveratrol considerably enhanced cardiac output by increasing Nrf2 expression, and considerably enhancing the host survival (Gorbunov et al., 2012). Resveratrol in the same animal model also attained the same effect through gavage (Gurusamy et al., 2010).

In Ang II caused cardiac remodeling and heart failure rat model, by increasing the stimulation of the Nrf2 pathway, organosulfur allucin administration prevented the development and progression of cardiac remodeling and hypertrophy (X.-H. Li et al., 2012).

Butein and phloretin are natural aromatic ketones of the flavonoids family and have established antioxidant and anti-inflammatory actions. It was demonstrated that butein and phloretin prevent oxidative injury via upregulation of HMOX1 and glutamate-cysteine ligase catalytic subunit (GCLC) expression via ERK2/Nrf2 signaling pathway (Yang et al., 2011).

Synthetic

MG132 is a peptide aldehyde which functions as a reversible proteasome inhibitor (Kisselev & Goldberg, 2001). While treating cells with MG132, decreased cleavage of ubiquitin bound Nrf2 was noted. Many shreds of experimental observations have revealed that MG132 can safeguard tissues from oxidative stress, as it can stimulate and activate the Nrf2-ARE signaling, causing the detoxifying and antioxidant genes to become upregulated (Dreger et al., 2009), (Sahni et al., 2008). MG132 could check hypertension and cardiac dysfunction caused by type 2 diabetes and heart hypertrophy, fibrotic scarring, oxidative injury, and inflammation (Bai et al., 2013), (Yuehui Wang et al., 2013). Administration of MG132 substantially reduced cardiac hypertrophy and fibrotic scarring in heart, besides enhancing cardiac output, in pressure-overload stimulated rodent heart failure models (B. Chen et al., 2010), (Y. Ma et al., 2013). MG132 may also inhibit inflammation due to NF- κ B (Cui et al., 2013).

RTA-402 is an active, Nrf2 inducer whose clinical trials are under process. It is a semi-synthetic methyl ester terpenoid obtained from natural constituent oleanolic acid. The imidazole derivative of RTA-402 stimulated Nrf2 in the heart and several organs when given orally in mice (Zhou et al., 2014). A phase III RTA-402 clinical trial was conducted, which was aimed to cure diabetic renal dysfunction in the late stage. However, because of RTA-402's toxic nature and high mortality owing to heart failure, this trial was concluded early. The drug was mechanistically revealed to facilitate sodium retention and cause hypertension by modification in the endothelin pathway in subjects with late-stage chronic renal failure (Zhou et al., 2014).

4-HNE is a α , β -unsaturated aldehyde synthesized by lipid peroxidation in cells. Treatment with 4-HNE activates cardiac Nrf2 and enhances the glutathione levels in the myocardial cells, thus correcting the functional revival of the left ventricle after ischemia-reperfusion injury in isolated perfused heart assay as well as reduced infarct size and prevented heart muscle cell death in-vivo (Y. Zhang et al., 2010). In Nrf2 knockout mice, the cardioprotective action of 4-HNE was not detected, suggesting that this defense is based on Nrf2 (Y. Zhang et al., 2010).

CONCLUSION

Enhanced heart muscle ROS production results in augmented necrosis and cell death that lead to heart remodeling and dysfunction. Patients whose cardiovascular system has inadequate levels of Nrf2 are more susceptible to heart failure. The antioxidant system of Nrf2 has a big part in cellular protection against free radical disruption, whereas lack of Nrf2 reliant gene expression is implied in several aspects and phases of cardiovascular disorders. Improvement of Nrf2 expression might be advantageous in diabetic cardiomyopathy, mitochondrial syndrome, myocardial infarction and decrease of the consequences of the aging of the cardiac tissue; though, the possible attenuation of Nrf2 controlled inflammatory activation in macrophages having plaques, together with the fatality of KEAP1 knockout mice, poses a warning to the pharmacological stimulation and activation of Nrf2 as a therapeutic strategic move. Nrf2 target genes like HMOX1 could be selectively upregulated to deliver a more responsive therapeutic strategic approach. Several components of the nutritional diet have inducers of Nrf2. Apart from the progressed knowledge of rational design and high-throughput screening to pick out ideal Nrf2 stimulating chemical compounds, nature may have already performed the task.

Nevertheless, a pharmaceutical drug that can activate Nrf2 expression for heart disorder therapy remains to be detected or systematically executed. Nrf2 may coordinate a range of antioxidants and further cytoprotective genes to deliver a defense mechanism against heart dysfunction caused by unfavorable stresses. Further research, though, is required to comprehend more fully the responsibility of Nrf2 in the pathogenesis of ventricular remodeling and heart failure beforehand, it can be genuinely regarded as a therapeutic target for various cardiac disorders.

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