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Nrf2-Keap1 Activation as A Potential Target of the Antioxidant Defense System in Diabetes Mellitus

Diabetes Mellitus'ta Nrf2-Keap1 Aktivasyonu, Antioksidan Savunma Sisteminin Potansiyel Bir Hedefidir

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia and complications that include micro and macrovascular disease. Nrf2 and its endogenous inhibitor, Keap1, function as a ubiquitous, evolutionarily conserved intracellular defense mechanism to counteract oxidative stress. Sequestered by cytoplasmic Keap1 and targeted to proteasomal degradation in basal conditions, in case of oxidative stress Nrf2 detaches from Keap1 and translocates to the nucleus, where it heterodimerizes with one of the small Maf proteins. Oxidative stress is the major pathogenic factor in diabetes and is mediated by Nrf2, a master regulator of the antioxidant protection response. Nrf2-induced antioxidant metabolic pathways include enzymes for the production, utilization, and regeneration of reduced glutathione (GSH). The Keap1/Nrf2 signaling pathway can effectively suppress intracellular ROS overproduction and protect pancreatic β-cells from oxidative stress-induced DNA damage, contributing to the suppression of T1DM development. However, inhibition of the Keap1/Nrf2 signaling pathway significantly promoted the progression of T1DM. It has been suggested that Nrf2-related epigenetic changes reduce the occurrence and progression of diabetic complications by inhibiting oxidative stress. Various antioxidants such as A, E, and C vitamins, carotenoids, and minerals like zinc, manganese, copper, iron, and selenium are essential for the activity of Nrf2 also the natural antioxidants such as curcumin and flavonoids found in vegetables, fruits, and edible herbs also play an important role in activating the Nrf2 signaling pathway. In this review, we summarize the role of oxidative stress in diabetic pathogenesis and the role of antioxidants in the regulation of Nrf2 in the treatment of diabetic mellitus.

Keywords: Diabetic Mellitus, oxidative stress, NRF2- Keap1, antioxidant, diabetic complication.

ÖZET

Diabetes mellitus (DM), hiperglisemi ile karakterize kronik bir hastalık olup mikro- ve makrovasküler komplikasyonları bulunmaktadır. Nrf2 ve endojen inhibitörü Keap1, oksidatif stresle mücadelede yaygın, evrimsel olarak korunmuş hücresel bir savunma mekanizması olarak işlev görür. Nrf2, sitoplazmik Keap1 tarafından tutulur ve bazal koşullarda proteazomal bozulmaya hedeflenir. Oksidatif stres durumunda Nrf2, Keap1'den ayrılır ve çekirdeğe taşınarak burada küçük Maf proteinleri ile heterodimer oluşturur. Nrf2 tarafından düzenlenen oksidatif stres diyabetin ana patojenik faktörü olup, antioksidan savunmanın ana düzenleyicisidir. Nrf2 tarafından indüklenen antioksidan metabolik yollar, glutatyon (GSH) üretiminde, kullanımında ve rejenerasyonunda azalma ile ilgili enzimleri içerir. Nrf2'nin oksidatif, enflamatuvar ve apopitotik etkilerinin olduğu gösterilmiştir. Keap1/Nrf2 sinyal yolağının, pankreatik β-hücrelerini oksidatif stres kaynaklı DNA hasarından koruyarak T1DM gelişimini engellediği gösterilmiştir. Bununla birlikte, Keap1/Nrf2 sinyal yolağının inhibisyonu, T1DM'nin oluşumunu stimüle etmiştir. Nrf2 ile ilişkili epigenetik değişikliklerin, oksidatif stresi inhibe ederek diyabetik komplikasyonların oluşumunu ve ilerlemesini azalttığı öne sürülmüştür. Ayrıca A, E, C vitaminleri ve karotenoidler gibi vitaminler ile çinko, mangan, bakır, demir ve selenium vb. mineraller gibi çeşitli antioksidanlar Nrf2'nin aktivitesi için esastır. Sebzelerde, meyvelerde ve yenilebilir otlarda bulunan doğal antioksidanlar da Nrf2 sinyal yolağının aktive edilmesinde önemli rol oynarlar. Bu derlemede, diyabetik patogenezde oksidatif stres ve diabetes mellitus tedavisinde Nrf2'nin düzenlenmesinde antioksidanların rolü özetlenmiştir.

Anahtar kelimeler: Diabetes Mellitus, Oksidatif stres, NRF2- Keap1, Antioksidan, Diyabetik komplikasyon.

Introduction

Oxidative stress

Oxidative stress is a lack of balance between prooxidative and antioxidative species. Reactive oxygen species are necessary in limited amounts for cell homeostasis and redox signaling[1]. Reactive oxygen species (ROS) are constantly produced in aerobic organisms as by-products of normal oxygen metabolism and include free radicals such as the superoxide anion (O2−) and the hydroxyl radical (OH-) as well as the non-radical hydrogen peroxide (H2O2). The superoxide anion is a common precursor of ROS and is involved in two pathways: i) rapid conversion to hydrogen peroxide and oxygen by superoxide dismutase (SOD) and ii) generation of highly toxic peroxynitrite by reaction with nitric oxide in addition, hydrogen peroxide can be converted to hydroxyl radicals, especially in the presence of transition metals such as iron and cobalt[2].

ROS are currently produced in the body in limited amounts and are necessary for maintaining cell homeostasis, signal transduction, gene expression, receptor activation, pathogen recognition, ensuring cell viability, proliferation, migration, and differentiation[3]. Oxidative stress as excessive ROS production, combined with weak protective mechanisms, leads to damage to important biomolecules[4].

Chronic oxidative stress is associated with post-translational oxidative changes in important biomolecules: lipid peroxidation, protein carbonylation, formation of carbonyl (aldehyde/ketone) adduct formation, nitration, sulfoxidation, DNA damage such as strand breaks or nucleobase oxidation leading to 8-oxo-20-deoxyguanosine. All these changes interfere with physiological redox signaling, leading to impaired H2O2 signaling in vital cellular processes[5].

Oxidative stress has been shown to be involved in a variety of diseases, including atherosclerosis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease, cancer, cardiovascular disease and diabetes mellitus, which has revealed the multiple mechanisms by which oxidants contribute to cellular damage[6].

Reactive oxidants are balanced by complex antioxidant defense systems that are regulated by a network of signaling pathways to ensure that the response to oxidants meets the body's needs. A recurring theme in oxidant signaling and antioxidant defense is reactive cysteine thiol–Based redox signaling. Nuclear Factor Erythroid 2–Related Factor 2 (Nrf2) is a novel regulator of cellular resistance to oxidants. Nrf2 controls the basal and induced expression of several antioxidants–dependent genes and thus regulates the cellular resistance to oxidants[7].

Production of ROS in the human body

ROS can arise either from exogenous sources such as environmental factors such as smoking, alcohol consumption, poor diet, X-rays, ozone pollution, radiation and toxins or from endogenous sources such as various cellular organs such as mitochondria, peroxisomes and the endoplasmic reticulum where oxygen consumption is high[8].

In the mitochondria, the mitochondrial electron transport chain (ETC) ensures that the electrons obtained during intermediate metabolism (glycolysis and Krebs cycle) are converted into O2. The electron transfer steps in complexes I, III and IV are coupled to the proton shift through the inner membrane. This creates an electrochemical gradient that is used by complex V to synthesize ATP from ADP and inorganic phosphate[9].

In peroxisomes, the respiratory pathway involves the transfer of electrons from various metabolites to oxygen, leading to the formation of H2O2 but is not coupled to oxidative phosphorylation to generate ATP, instead free energy is released in the form of heat. Other free radicals formed in the peroxisomes include H2O2, O2-- OH- and NO-. The β-oxidation of fatty acids is the most important metabolic process in which H2O2 is formed in the peroxisomes[10]. The various peroxisomal enzymes such as acyl-CoA oxidases, D-amino acid oxidase, L-α-hydroxy oxidase, urate oxidase, xanthine oxidase, D-aspartate oxidase have been shown to produce various ROS[11].

In the endoplasmic reticulum (ER), hydrogen peroxide (H2O2), a non-radical ROS, is generated by the process of oxidative folding. The utilization and dysregulation of H2O2 generated in the ER affects not only cellular homeostasis but also the longevity of organisms.

Endoplasmic reticulum stress (ERS) arises after the accumulation of misfolded proteins in the ER. ERS can reduce the production of functional proteins and even lead to apoptosis. To relieve the cell from ERS, an evolutionarily conserved mechanism called the unfolded protein response (UPR) is activated[12]

The process of protein folding supported by oxidase-1 of the endoplasmic reticulum leads to the production of ROS in the lumen of the endoplasmic reticulum. The production of ROS exceeds the quenching capacity of the antioxidant systems and disrupts ER homeostasis. ERS also induces the production of cytokines that lead to inflammatory reactions. This has been shown to be a major cause of various pathophysiological conditions compared to other cellular triggers in disease, resulting in increased oxidative stress, mitochondrial dysfunction and altered inflammatory responses that are detrimental to cell physiology and homeostasis[13]. On the other hand, ROS are also produced in biological systems such as cell signaling and the immune system.

Antioxidants

Antioxidants are essential for reducing oxidative processes and the negative consequences of reactive oxygen species (ROS) in the human body and food systems[1], In another definition, an antioxidant is defined as a substance that directly scavenges ROS or indirectly acts to up-regulate antioxidant defenses or inhibit ROS production[14].

Antioxidants are classified as enzymatic and nonenzymatic antioxidants[15,16].

Enzymatic antioxidants include Superoxide dismutase (SOD) is an enzyme that breaks down superoxide anion radicals into hydrogen peroxide. Glutathione peroxidase (GPX) breaks down hydrogen peroxide and hydroperoxides at the expense of glutathione. Catalase breaks down hydrogen peroxide to produce water and molecular oxygen, which is then converted to water with the help of cofactors like iron, zinc, copper, and manganese.

On the other hand, nonenzymatic antioxidants consist of ubiquinone, bilirubin, ferritin, lactoferrin, vitamin C, carotenoids, curcumin tocopherols, phenolics (both flavonoids and non-flavonoids), uric acid, alpha-lipoic acid, and ubiquinone[17]. ROS damage can be mitigated by both enzymatic and non-enzymatic antioxidants. They are carefully segregated in the cytoplasm and organelles (such as mitochondria) to attain the highest level of protection[18].

Diabetes mellitus pathogenesis and oxidative stress

Oxidative stress plays a crucial role in the development and advancement of diabetes and its related complications. The disparity between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms results in cellular damage and dysfunction. Oxidative stress in diabetes is exacerbated by persistent hyperglycemia and mitochondrial dysfunction, which lead to increased generation of reactive oxygen species. Furthermore, diabetic vascular consequences such as retinopathy, nephropathy, and cardiovascular illnesses are partly caused by oxidative stress-induced blood vessel damage and compromised endothelial function. Strategies to mitigate oxidative stress in diabetes include antioxidant therapy, lifestyle modifications, and effective management of hyperglycemia[19].

Numerous theories have been put out over the past century to explain the genesis of issues related to diabetes. AGEs, or advanced glycation end products, are among them[20]. Oxidative stress[21], pseudohypoxia, true hypoxia, carbonyl stress, and polyol pathway activation[22] increased protein kinase C activity[23], as well as modifications to lipoprotein metabolism. Various of antioxidants can reduce of diabetic complications by targeting of these pathways which include Insulin therapy for rats with streptozotocin-induced diabetes improved oxidative damage and obstructed the progress of oxidative stress[24].

There have been reports of Sulforaphane SFN's positive benefits on DM complications. SFN inhibited the effects of diabetes-induced oxidative stress, inflammation, apoptosis, cell proliferation, thickness of the

tunica media and collagen buildup in the aorta in a mouse model of type 2 diabetes via activating NRF2 antioxidant signaling in the aorta[25]. Curcumin may mitigate the polyol pathway by lowering sorbitol buildup and oxidative damage. Furthermore, it could prevent protein kinase C (PKC) from being activated, which would lessen retinal inflammation and vascular anomalies[26]. They could also change the hexosamine pathway by preventing the generation of AGEs, which are connected to retinal degeneration[27]. This may be one of the ways that the antioxidant does this.

NRF2-KEAP1 pathway

Nuclear factor erythroid 2-related factor or Nrf2, is a transcription factor belonging to the Cap'n'collar (CNC) family. It has 605 amino acids and is separated into seven functional domains that are highly conserved, referred to as Neh1–Neh7 (Figure 1a). While the Neh5 domain oversees Nrf2's cytoplasmic localization, the N-terminal domain affects the stability and ubiquitination of Nrf2 by its negative regulator Keap1[28].

The cap 'n' collar basic-region leucine zipper (bZIP) domain of the Neh1 domain controls DNA binding, whereas the nuclear localization signal (NLS) oversees Nrf2's nuclear translocation[29]. Transactivation domains Neh3, Neh4, and Neh5 mediate Nrf2's interaction with other coactivators. Negative regulatory domain Neh6 with serine-rich residues interacts with β-transducin repeat-containing protein (β-TrCP) and ubiquitinates Nrf2. By encouraging Nrf2 to attach to the retinoic X receptor α (RXRα), the Neh7 domain suppresses the Nrf2-ARE signaling pathway[30-28-31].

Kelch-like ECH-associated protein 1 (KEAP1), an E3 ligase adaptor, is primarily responsible for controlling NRF2 stability. A wide complicated, tramtrack, bric-a-brac (BTB) homodimerization domain, an intervening region (IVR), and a C-terminal Kelch domain with a double glycine repeat (DGR) make up the three functional domains of the homodimer protein KEAP1 (Figure 1(b)). The NRF2 Neh2 domain and the Kelch domain bind at the DLG and ETGE amino acid sequences. The ETGE motif has approximately 100 times greater affinity for KEAP1 than the DLG motif, according to isothermal calorimetry experiments[32]. NRF2 is presented by KEAP1 for ubiquitination by the E3 ligase complex (CUL3/RBX1), which is then followed by NRF2 degradation by the proteasome 26S[33].

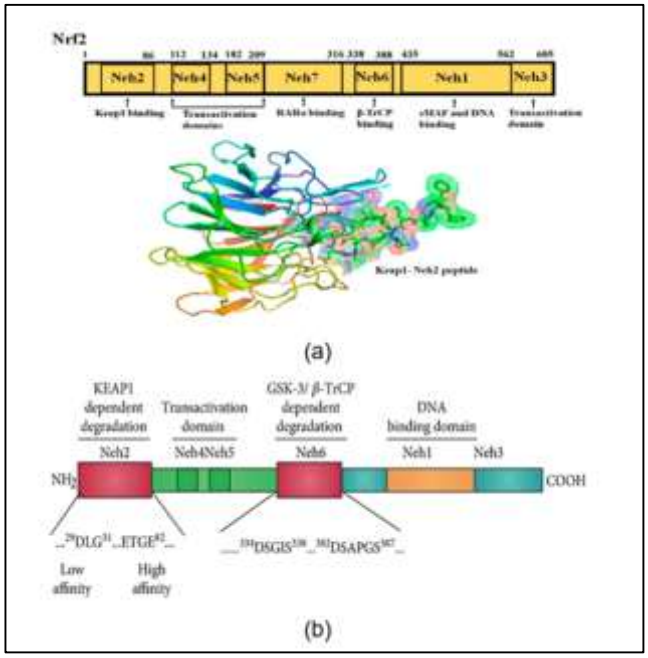

Figure 1a, b. Schematic representation showing how the peptide from the Neh2 domain of Nrf2 (sticks in mesh) presents the surface of the Kelch domain (carton) in crystal structures[28].

To maintain low NRF2 abundance at baseline settings, KEAP1 easily sequesters NRF2 and tethers it for ubiquitination and proteasomal destruction [34] .Stress causes KEAP1 to change on a few cysteine moieties, which stops the protein's ability to function as an E3 ligase adaptor. As a result, de novo protein synthesis stabilizes and increases NRF2. NRF2 will go into the nucleus and escape KEAP1's sequestration when its abundance surpasses that of KEAP1 [35]. NRF2 forms transcriptionally active heterodimers with small musculoaponeurotic fibrosarcoma (sMaf) proteins in the nucleus[36] .Certain antioxidant response elements (ARE) in the promoters of a variety of target genes, such as antioxidant and phase II detoxification, are recognized by the NRF2-sMaf heterodimer [37].

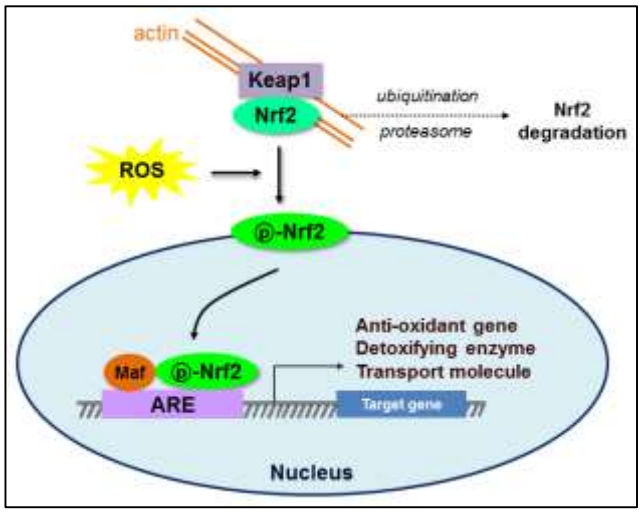

Figure 2. Schematic diagram of the Nrf2-Keap1-ARE signaling pathway [38]

NRF2-KEAP1 activation of the antioxidant defense in the cell

Since Nrf2 activates a cascade of events aimed at mitigating the oxidative stress induced by ROS, it is referred to as the master regulator of the antioxidant cytoprotective response[39]. A system of collaborating enzymes engaged in phase I, II, and III drug detoxification processes as well as the metabolic removal of pro-oxidants is formed by NRF2 activated multi-antioxidant genes[40]. Phase I enzymes mediate the oxidation, reduction and hydrolysis of various xenobiotics and include Aldo-keto reductases (AKRs), carbonyl reductases (CBRs), aldehyde dehydrogenase 1 (ALDH1), NAD(P)H quinone oxidoreductase 1 (NQO1) and various cytochrome P450s (CYPs), such as CYP2a5 and CYP2b6[41].

Nrf2 regulates glutathione synthesis and metabolism. This element is crucial as a non-enzymatic antioxidant because it can donate electrons, reducing the disulfur links of cysteine amino acids in cytoplasmic proteins[42].

NRF2 induces general antioxidant pathways, including enzymes for the production, utilization, and regeneration of reduced glutathione (GSH). The three NRF2 targets involved in GSH synthesis are glutamate-cysteine ligase catalytic (GCLC) and modulator (GCLM) subunits, as well as glutathione synthetase (GSS)[43].

Glutathione reductase (GR) facilitates the reduction of glutathione to regenerate GSH using NADPH as a cofactor. These cytoprotective proteins, encoded by NRF2-target genes, protect against toxic and oxidative insults and are crucial in combating diseases with oxidative stress as a pathological feature, such as cardiovascular disease, metabolic syndrome, neuronal degeneration, autoimmune disorders, and cancer[44].

Many original studies have shown the protective role of NRF2. In a study using rats, Younis et al. extended these observations by demonstrating that geraniol, an Nrf2-activating phytochemical, has protective effects

on oxidative, inflammatory, and apoptotic alterations in isoproterenol-induced myocardial infarction. Similar to the aforementioned studies, the involvement of Keap1/Nrf2 signaling is indirectly inferred by the induction of antioxidant and cytoprotective genes [44]. In another study Guerrero-Hue et al. review the protective roles of Nrf2 in renal disease[45]. This is a topic of significant clinical interest but also controversy, as a major phase 3 clinical trial of bardoxolone methyl in patients with chronic kidney disease and diabetes mellitus was stopped early due to a higher risk of heart failure and cardiovascular events[46].

Lou et al. verify in study, The Keap1/Nrf2 signaling pathway effectively suppresses ALX-stimulated intracellular ROS overproduction, protecting pancreatic β-cells from oxidative stress-induced DNA damage, and contributing to the suppression of T1DM development. Conversely, inhibiting the Keap1/Nrf2 signaling pathway significantly promotes the progression of T1DM[47].

NRF2 in diabetes mellitus and diabetic complications

Metabolic diseases like type 2 diabetes (T2D) are caused by a confluence of environmental, behavioral, and genetic factors. Oxidative stress is a major factor in the pathophysiology of type 2 diabetes (T2D), namely in insulin resistance and pancreatic β-cell dysfunction. Reactive oxygen species (ROS) are deadly, but they also serve as crucial intracellular signaling molecules in glucose sensing and insulin signaling[48]. Long-term diabetic conditions can lead to diabetic complications due to an imbalance in metabolites, specifically carbohydrates and lipids. This imbalance ultimately affects the microvascular and cardiovascular systems[49].

The pathological features of DM and its associated complications have been extensively researched. Specifically, oxidative stress, apoptosis, and inflammation have been recognized as contributing factors to the development of DM-induced complications. Nrf2 plays a crucial role in maintaining cellular redox balance and activating antioxidant enzymes. Dysregulation of Nrf2 signaling has been noted in various human diseases, including DM. The potential of targeting Nrf2 for the treatment of DM and its complications has been the subject of numerous studies[50].

NRF2-correlated epigenetic modifications have been suggested to reduce the occurrence and advancement of DM-related cardiac and vascular complications by inhibiting oxidative stress[51]. Recent research indicates that NRF2-related epigenetic alterations may protect against diabetic blood-brain barrier (BBB) damage by acting as antioxidants and anti-inflammatory agents. According to Zhao et al. the miR-200a/Keap1/NRF2 signaling pathway was triggered by HDAC3 inhibition, which attenuated the inflammatory response and improved the permeability of the blood-brain barrier caused by diabetes[52]. Besides, the Keap1/NRF2 axis has been reported to be regulated by miR-200a-3p/141-3p in diabetic renal mesangial cells, suggesting that these miRNAs are involved in reducing oxidative stress and protecting against DN[53].

According to Song et al., omentin-1 can increase the levels of antioxidant enzymes catalase and superoxide dismutase (SOD) and reduce the expression of oxidative stress indicators malondialdehyde, interlukin-8, tumor necrosis factor-α, and monocyte chemotactic protein 1. By decreasing miR-27a binding to the NRF2 3' untranslated region (UTR) in type II DN, omentin-1 can downregulate miR-27a to boost the production of NRF2, according to further mechanistic study[54].

Additionally, some research showed that diabetic artery damage may be significantly impacted by miRNA control of NRF2. For example, in HG-stimulated vascular smooth muscle cells (VSMCs) , miR-24 has been demonstrated to activate the NRF2/HO-1 signaling pathway to avoid oxidative damage[55].

The primary regulator of cellular defenses against hazardous oxidative stress levels is Nrf2. Nrf2 is required for the maintenance of β cell mass and the survival, proliferation, and function of β cells. In fact, Nrf2 activation lowers body weight, improves insulin sensitivity, decreases inflammation, and maintains β cell mass. For this reason, a variety of pharmacological Nrf2 activators are being investigated in clinical studies to treat diabetes and its consequences[56].

Activation of NRF2 by natural antioxidants

Many different bioactive substances that can activate the Nrf2 signaling pathway and have positive health benefits are present in the human diet. They have a substantial correlation with a lower chance of developing

several chronic illnesses, including cancer, Alzheimer's disease, and atherosclerosis. They consist of carotenoids and vitamins A, E, and C. Additionally, some minerals such as copper, iron, zinc, manganese, and selenium are necessary for the antioxidant enzymes to function. Moreover, flavonoids, curcumin, and dietary polyphenols are regarded as strong antioxidants. The best sources of these antioxidants include fruits, vegetables, and edible plants [57].

One explanation for the antioxidant properties of the vitamin A and carotenoids is a hydrophobic polyene chain that reacts with peroxyl radicals to capture singlet oxygen

[58]. Bile duct ligation (BDL) rats were given vitamin A, which triggered Nrf2/ARE signaling and enhanced antioxidant mechanisms. The administration of vitamin A supplements has the potential to enhance vitamin A status in BDL rats, as well as operate as a Nrf2 activator and mitigate cholestasis liver damage [59].

In human atopic asthmatics in vivo, vitamin E can restore Nrf2 activity that was diminished in alveolar macrophages during the last stage of IgE-mediated inflammation. Age-dependent variations were seen in the effects of vitamin E treatment, which promoted downregulation of the IkB-NFκB pathway and EPx expression to lower ROS generation and eosinophil activation[60].

Numerous studies demonstrate curcumin's many advantageous qualities, which include the anti-inflammatory, anti-diabetic, anti-oxidant, anti-microbial, anti-arthritic, anti-carcinogenic, and wound-healing capabilities[61].

Curcumin has antioxidant action due to its ability to donate hydrogen and scavenge free radicals. In addition, curcumin inhibits the activities of xanthine oxygenase, lipo and cyclo-oxygenases, nitric oxide production and reactive oxygen species (ROS). Additionally, curcumin suppresses the synthesis of pro-inflammatory cytokines that are produced from macrophages and monocytes, such as tumor necrosis factor-α (TNF-α) , interleukin-8 (IL-8), monocyte inflammatory protein-1 (MIP-1) , monocyte chemotactic protein-1 (MCP-1), and interleukin-1b (IL-1b)[62].

Garlic oil contains DATS, an organosulfur, as one of its main ingredients. DATS appears to be mediated by alteration of the Keap1 Cys288 residue since it activates Nrf2 and stimulates HO-1 and NQO1 expression in both in vitro and in vivo investigations[63].

The discovery that natural compounds, such as sulforaphane from broccoli sprouts, can activate the Nrf2 pathway [64]. Other research has looked into synthetic Nrf2 activators, such as in diabetic nephropathy[46].

Resveratrol inhibits platelet aggregation, lipoprotein oxidation, apoptosis, and cardiac problems via controlling glucose metabolism, which lowers insulin resistance[65]. Furthermore, the prevention and treatment of diabetic complications have been linked to its ability to scavenge free radicals[66].

The micronutrients zinc (Zn), chromium (Cr), and vitamin D stimulate the production of antioxidant enzymes. Zinc activated NADPH quinone oxidoreductase-1, catalytic and modulatory subunits of gamma glutamate cysteine ligase and HO-1 in a renal proximal tubular cell line (NRK-52E cells) via increasing nuclear Nrf2 and decreasing cytosolic Keap1[67]. Interestingly, Cr treatment raised a brain Nrf2 and decreased inflammation via NF-κB suppression in male Wistar-STZ rats given a high-fat diet[68]. Finally, in ventricular heart tissue of rats that were made hyperglycemic by alloxan, l-arginine, an important amino acid, reduced cardiomyopathy by upregulating Nrf2 gene expression[69].

Conclusion

In conclusion, these articles highlight the important role of the NRF2-KEAP1 pathway in protecting cells from oxidative stress and its implications in various diseases, especially for diabetes and its complications. NRF2 is essential for cellular redox balance and activation of antioxidant enzymes in diabetes. Dysregulation of NRF2 signaling has been implicated in diabetes and its complications, making it a potential therapeutic target. Several metabolites found in the human diet, such as carotenoids, vitamins, flavonoids, curcumin, and minerals can activate the NRF2 pathway The NRF2-KAAP1 pathway is expressed as an important component in cells into protective mechanisms to combat oxidative stress internally, and understand how it works with regulatory Naam, to prevent Developing strategies hold great promise.

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