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Recent Advances in the Pathogenesis of the Nrf2ARE Signaling Pathway in Diabetic Nephropathy and Its Treatment with Traditional Chinese and Western Medicine

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Abstract: ***Diabetic nephropathy (DN) is the most serious microvascular complication of diabetes and the leading cause of end-stage renal disease. Its core pathological mechanism is closely related to persistent oxidative stress. The Nrf2/ARE signaling pathway is the most important endogenous defense hub against oxidative damage in the body, and its homeostasis imbalance directly drives key pathological processes such as podocyte injury, renal tubular epithelial–mesenchymal transition, renal interstitial fibrosis, and mitochondrial dysfunction-mediated ferroptosis. Therefore, targeting the Nrf2/ARE pathway and restoring renal redox homeostasis has become a highly promising therapeutic strategy for delaying DN progression. This article systematically reviews the biological characteristics of the Nrf2/ARE pathway and its pathological role in DN, with a focus on research progress in interventions targeting this pathway using both traditional Chinese and Western medicine. It is expected to provide more precise and efficient novel therapeutic strategies for overcoming DN and accelerate the translation from basic research to clinical application.***

Keywords: Diabetic nephropathy, Nrf2/ARE signaling pathway, Oxidative stress, Traditional Chinese medicine.

1. Introduction

Diabetic nephropathy (DN) is one of the most common and serious microvascular complications of diabetes [1]. With the global prevalence of diabetes soaring, the incidence of DN remains high, resulting in elevated rates of disability and mortality, and imposing a substantial economic burden. Typical pathological features of DN include thickening of the glomerular basement membrane, expansion of the mesangial matrix, podocyte loss, renal tubulointerstitial fibrosis, and eventual glomerulosclerosis [2]. Although multiple clinical interventions are currently available, such as strict glycemic and blood pressure control, along with the widespread use of renin-angiotensin system (RAS) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors, these treatments primarily focus on improving hemodynamics and controlling metabolic parameters, and still possess notable limitations.

Numerous studies indicate that oxidative stress (OS) is a central pathogenic mechanism in the onset and progression of diabetic nephropathy (DN) [3]. Driven by chronic hyperglycemia, dyslipidemia, and hemodynamic abnormalities, excessive reactive oxygen species (ROS) are generated in the kidneys, particularly within mitochondria, leading to a dynamic imbalance between oxidation and antioxidation. Excessive ROS not only directly damages lipids, proteins, and DNA but also acts as a second messenger to activate various inflammatory pathways, such as PKC, NF-κB, and TGF-β, thereby triggering inflammatory responses, apoptosis, ferroptosis, and fibrosis [4]. Within the body's antioxidant defense network, the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signaling pathway, which is composed of Nrf2 and its downstream ARE, represents the most critical endogenous defense system currently known [5]. Moreover, Nrf2 can regulate the expression of various antioxidant enzymes, detoxifying enzymes, and metabolism-related genes. In the pathological environment of DN, the activation status of the Nrf2/ARE pathway directly determines the ability of renal cells to resist high-glucose toxicity and oxidative damage. Thus, the biological characteristics, dynamic evolution patterns, and mechanisms of renal pathological damage mediated by the Nrf2/ARE pathway in DN.

2. Mechanisms of the Nrf2/ARE Pathway in the Progression of Diabetic Nephropathy

2.1 Homeostatic Maintenance Mechanism of the Nrf2/ARE Pathway

The core mechanism of the Nrf2/ARE pathway relies on the Keap1-Nrf2-Cul3 E3 ubiquitin ligase complex. Keap1 is a cysteine-rich cytoplasmic protein that acts as a substrate adaptor, forming an E3 ubiquitin ligase complex with Cullin 3 and a RING finger protein. Under physiological conditions, Keap1 mediates the polyubiquitination of Nrf2 by the Cul3 E3 ubiquitin ligase, maintaining intracellular free Nrf2 protein at extremely low levels and preventing excessive expression of antioxidant genes from interfering with normal redox signaling. When cells undergo mild oxidative stress, the Nrf2/ARE pathway can be activated, disrupting the interaction between Keap1 and Nrf2. This leads to the deubiquitination of newly synthesized Nrf2, its accumulation in the cytoplasm, nuclear translocation, and specific binding to target gene promoters. This binding rapidly initiates the transcriptional expression of a series of "self-rescue" programs downstream, including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and others. These antioxidant and detoxifying enzymes work synergistically to efficiently clear intracellular ROS and toxic metabolites, restoring cellular redox homeostasis [6].

2.2 Decompensation and Dysfunction of the Nrf2/ARE Pathway in the Diabetic State

Although the Nrf2/ARE pathway exerts protective effects on cells under acute or mild stress, in the chronic pathological environment of diabetes, it can lead to decompensation of this pathway, ultimately resulting in dysfunction. Under prolonged hyperglycemic conditions, advanced glycation end-products (AGEs) are generated in large quantities and can bind to the receptor for AGEs (RAGE), while hyperglycemia directly triggers excessive activation of the protein kinase C (PKC) pathway, initiating intracellular signal transduction cascades. These pathological signals can enhance the affinity of Keap1 for Nrf2 and promote its ubiquitin-mediated degradation, leading to a failure to initiate the antioxidant response. In the early stages of DN, renal cells may transiently exhibit compensatory activation of Nrf2 to counteract initial oxidative damage. However, as the disease progresses, the sustained oxidative stress from persistent hyperglycemia exceeds the compensatory capacity of the Nrf2 system, leading to a decline in its transcriptional activity or a blunted response of its downstream target genes to Nrf2, which can accelerate the deterioration of DN [7]. Studies have shown that in heavy metal-induced renal injury models, sustained non-canonical activation of Nrf2, mediated by impaired p62-dependent autophagic degradation of Keap1, exacerbates renal damage by promoting apoptosis and inhibiting autophagy, playing a detrimental role [8]. This suggests that in chronic kidney diseases such as DN, disruption of the Nrf2 pathway is not only manifested as insufficient antioxidant capacity but may also involve abnormal accumulation and functional alteration of Nrf2 due to mechanisms such as impaired autophagy. Therefore, restoring the physiological rhythm and appropriate activation of the Nrf2/ARE pathway represents a rational strategy for treating DN.

3. Mechanisms of Renal Pathological Injury Mediated by the Nrf2/ARE Pathway and Drug Intervention Targets

3.1 Podocyte Injury and the Protective Role of Nrf2

Podocytes are highly differentiated terminally differentiated cells. Their injury in diabetic nephropathy (DN) serves as the initiating factor and central link leading to the occurrence of proteinuria and glomerulosclerosis. The high-glucose environment can cause mitochondrial dysfunction in podocytes, resulting in a burst generation of large amounts of reactive oxygen species (ROS), leading to foot process effacement, flattening, or even disappearance [9]. Simultaneously, oxidative stress disrupts the integrity of the filtration barrier, causing the leakage of large amounts of plasma proteins and the formation of proteinuria. Moreover, the long-term diabetic microenvironment can also induce cellular senescence in podocytes. Nrf2 can protect podocytes from high-glucose-induced damage. Activation of Nrf2 significantly upregulates the expression of antioxidant enzymes such as SOD and GSH-Px, effectively clearing ROS within podocytes and thereby protecting the stability of the cytoskeleton. Furthermore, Nrf2 can maintain podocyte polarity and survival by inhibiting pro-fibrotic and pro-apoptotic signaling pathways such as Notch [10]. Regarding podocyte senescence, studies have found that the ketone body β-hydroxybutyrate (β-HB) can significantly alleviate podocyte senescence and injury induced by the diabetic microenvironment. The mechanism lies in β-HB directly targeting and inhibiting the activity of GSK3β, a key kinase that negatively regulates Nrf2 activity, thereby enhancing the antioxidant transcriptional response of Nrf2, protecting podocytes from high-glucose toxicity, and ameliorating diabetic nephropathy and proteinuria [11]. Therefore, stabilizing and appropriately activating Nrf2 through pharmacological intervention is an important therapeutic target for reducing podocyte apoptosis, senescence, and proteinuria leakage.

3.2 Renal Tubular Epithelial Cell Injury and Interstitial Fibrosis

Tubulointerstitial lesions are a key driving factor in the progression of diabetic nephropathy (DN) to end-stage renal disease (ESRD). Renal tubular epithelial cells (TECs), which are rich in mitochondria, are susceptible to oxidative stress and endoplasmic reticulum stress induced by high glucose and protein overload [12]. Sustained stress leads to epithelial-mesenchymal transition (EMT) in TECs, characterized by downregulation of E-cadherin and upregulation of α-SMA and vimentin. This process is accompanied by the release of pro-fibrotic factors such as TGF-β1, which activate the Smad pathway, leading to excessive deposition of collagen and fibronectin in the interstitium, ultimately resulting in irreversible renal interstitial fibrosis [13]. Nrf2 is a key molecule in blocking TEC injury and fibrosis. Its main mechanisms include scavenging reactive oxygen species (ROS) to alleviate oxidative stress, antagonizing the TGF-β1/Smad3 pathway, or inhibiting transcription factors such as Snail/Slug to block the EMT process. Recent studies have shown that vitamin D receptor (VDR) agonists (e.g., paricalcitol) exert protective effects by activating the Nrf2/HO-1 signaling axis [14]. This pathway effectively inhibits ferroptosis in TECs by modulating iron metabolism, elevating glutathione (GSH) levels, and upregulating the expression of GPX4 and SLC7A11, thereby alleviating renal tubular damage and interstitial fibrosis.

3.3 Mitochondrial Dysfunction and Programmed Cell Death

Mitochondria are the primary source and initial target of reactive oxygen species (ROS). In diabetic nephropathy (DN), hyperglycemia induces mitochondrial dynamics imbalance (increased Drp1/Fis1; decreased Mfn1/2/Opa1), leading to mitochondrial fragmentation and respiratory chain dysfunction, which cause mtDNA damage and excessive ROS leakage, forming a vicious cycle of oxidative stress [15]. This damage not only induces apoptosis but also triggers ferroptosis—an iron-dependent programmed cell death characterized by lipid peroxide accumulation, which plays a central role in renal tubular injury in DN. Nrf2 counteracts these processes by maintaining mitochondrial quality control: on one hand, it upregulates antioxidant enzymes to scavenge ROS; on the other hand, it regulates PGC-1α to promote mitochondrial biogenesis. In terms of anti-ferroptosis, Nrf2, as a transcriptional regulator of GPX4 and SLC7A11 (a core component of System Xc-), exerts renoprotective effects [16]. Mechanistic studies have confirmed that Sirt1/PGC-1α can recruit Nrf2 to co-activate GPX4 transcription [17], and activation of the PPARα/Nrf2/GPX4–SLC7A11 axis can also effectively inhibit lipid peroxidation. Therefore, targeted intervention of the Nrf2 pathway to improve mitochondrial function and block ferroptosis represents an important therapeutic strategy for DN.

4. Research Progress on Traditional Chinese and Western Medicine Interventions for DN Based on the Nrf2/ARE Pathway

Diabetic nephropathy does not have an exact corresponding disease name in traditional Chinese medicine (TCM) classics. Based on its clinical manifestations, it is often categorized under "wasting-thirst disease", "edema", "block and repulsion", or "consumptive disease" [18]. Its pathogenesis is generally characterized by a deficiency of the root and excess of the branch. The root deficiency involves dual deficiency of qi and yin, as well as deficiency of the spleen and kidney. The branch excess includes blood stasis, water-dampness, and turbid toxins. Etiologically, it is often due to innate constitutional insufficiency, compounded by long-term dietary irregularities and overconsumption of rich, sweet, and fatty foods, which generate internal heat and consume qi and yin. Alternatively, emotional disturbances or excessive fatigue and desire can lead to dysfunction of the zang-fu organs. If the condition persists and fails to heal, it eventually affects the kidney.

4.1 Traditional Chinese Medicine Monomers and Active Components

Traditional Chinese medicine (TCM) contains a wealth of natural active compounds, such as flavonoids, salidroside, berberine, and astragaloside IV, which can activate the Nrf2-ARE signaling pathway. By modulating antioxidant stress injury mechanisms, they achieve the goal of delaying the progression of kidney disease and are widely used in the treatment of diabetic nephropathy (DN) within TCM. Wang Jing [19] found in a clinical study that astragaloside IV can alleviate high-glucose-induced HK-2 cell cytotoxicity and oxidative stress. The specific mechanism may involve regulating the Nrf2/ARE pathway and reducing the expression of the downstream gene L-FABP, thereby improving high-glucose-induced HK-2 cell toxicity and oxidative stress, thus providing a new target for the treatment of diabetic nephropathy. Han Gao [20] successfully screened puerarin from traditional herbal medicine and confirmed that it can effectively scavenge hydroxyl radicals (•OH) and protect damaged renal cells by activating the Sirt1/Nrf2/Keap1 signaling pathway. Zhang Xuesong [21] found in an animal experiment that salidroside can enhance the activation of the Nrf2/ARE signaling pathway in a rat model of diabetic nephropathy, induce γ-GCS expression, and inhibit PPAR-γ expression, thereby reducing blood glucose levels, decreasing proteinuria, and alleviating renal oxidative stress injury. Furthermore, salicylic acid, a defensive hormone widely present in the plant kingdom, plays a crucial role in plant immunity through its biosynthesis and signaling mechanisms [22]. Many TCM components rich in salicylic acid derivatives or similar phenolic structures also exhibit potential cross-activation effects on the Nrf2 pathway after entering the human body, which provides insights from plant biology for discovering new antioxidants from traditional Chinese medicine.

4.2 Traditional Chinese Medicine Compound Decoctions

Traditional Chinese medicine (TCM) compound formulas are the main form of clinical treatment for diabetic nephropathy (DN) in TCM. Their advantage lies in the compatibility of "sovereign, minister, assistant, and envoy" and the synergistic intervention of "multi-component, multi-target" mechanisms. Commonly used classic formulas and empirical prescriptions, such as Huangqi Tang, Tangshen'an, Guizhi Fuling Wan, and Shengqing Jiangzhuo Capsule, have shown good efficacy in both clinical and basic research. Song Ke [23], in an animal experimental study, investigated the therapeutic mechanism of the Yiqi Yangyin Huoxue Formula on diabetic nephropathy in rats based on the Nrf2/ARE pathway. It was found that the formula can downregulate Keap1 protein expression and upregulate Nrf2 and HO-1 protein levels, thereby enhancing the body's antioxidant stress capacity, alleviating renal pathological damage, and delaying renal fibrosis. Additionally, Wang Lu [24] used the compound Tangshen'an from the same mechanistic perspective and found that this formula activates the Nrf2/ARE signaling pathway in DN model rats, upregulates the expression of the antioxidant enzyme gene HO-1, inhibits the expression of NF-κB p65 mRNA and protein, improves renal inflammatory responses, and exerts antioxidant effects. Li Jiajie [25] reviewed the therapeutic mechanisms of Shenqi Dihuang Tang on DN, indicating that active components in Shenqi Dihuang Tang can activate the Nrf2/HO-1 signaling axis, upregulate the expression of antioxidant enzymes such as SOD and glutathione (GSH), and reduce ROS and MDA levels, thereby alleviating oxidative damage in the kidneys of DN. The material basis and pharmacological mechanisms of these traditional treatment principles are closely related to the activation of the Nrf2 antioxidant mechanism, reflecting the perfect integration of TCM macro-pattern differentiation and micro-molecular targets.

4.3 Western Medicine and Other Non-Traditional Chinese Medicine Approaches Targeting the Nrf2/ARE Pathway for the Treatment of DN

Modern medicine has made progress in intervention strategies targeting the Nrf2/ARE pathway, covering chemically synthesized drugs, natural nutrients, and nanodelivery systems. Among synthetic chemical agonists, bardoxolone methyl (CDDO-Me) binds to cysteine residues of Keap1 to release Nrf2. While it showed early potential in improving estimated glomerular filtration rate (eGFR), its clinical application is limited due to risks of heart failure and fluid retention, necessitating reassessment of patient selection and dosage. The curcumin derivative C66 demonstrates anti-DN activity in animal models by improving water solubility and bioavailability. Among natural compounds, sulforaphane (SFN) and the trace element zinc exert protective effects by activating the Nrf2/HO-1 axis and inhibiting Fyn kinase to maintain nuclear Nrf2 activity, respectively [26]. Proteasome inhibitors (e.g., MG132) upregulate signaling by blocking ubiquitin-mediated degradation of Nrf2. Although effective in basic experiments, they remain primarily in preclinical research due to toxicity from nonspecific inhibition. Nanotechnology provides new directions for precise therapy. pH-activatable platinum-sulfur cluster (Pt5.65S) pre-nanozymes release hydrogen sulfide (H2S) in the inflammatory microenvironment and convert to platinum nanozymes, significantly alleviating renal injury at low doses through an endogenous-exogenous synergistic antioxidant mechanism [27]. These strategies offer translational prospects for the treatment of DN.

5. Summary and Outlook

The pathological progression of DN is directly associated with the imbalance of Nrf2/ARE pathway homeostasis, which leads to podocyte injury, renal tubular fibrosis, and ferroptosis induced by mitochondrial dysfunction. Therefore, targeting the Nrf2/ARE pathway holds potential in DN therapy. Current intervention strategies exhibit complementary features between traditional Chinese and Western medicine: TCM monomers and compound formulas exert holistic regulatory effects by activating Nrf2 through multiple targets, while chemical agonists, marine-derived products, and nano-delivery systems (such as cerium oxide nanoparticles) focus on improving bioavailability and precise targeting [28]. However, current research still faces challenges such as insufficient mechanistic validation, complex compound formulations, and limitations in clinical translation. Addressing existing limitations, including insufficient targeting specificity, complex components, and clinical safety concerns, future efforts need to deeply integrate cutting-edge technologies for mechanistic elucidation. Multi-omics and molecular docking techniques can be utilized to clarify molecular details, and organoid models can be employed to accelerate drug screening [29]. Secondly, a systems biology perspective should be broadened. Attention should be paid to the gut–kidney axis regulation, indirectly activating the renal Nrf2 pathway by modulating the gut microbiota [30]. Exploring gut–kidney axis interactions and the translation of intelligent nanomedicines is essential to achieve precise treatment for DN.

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