PRACTICAL ASPECTS

Nonpharmacologic Strategies to Modulate Nuclear Factor Erythroid 2–related Factor 2 Pathway in Chronic Kidney Disease

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Nuclear factor erythroid 2–related factor 2 (Nrf2) is a transcription factor with a high sensitivity to oxidative stress, which regulates the expression of detoxifying enzymes, besides that, can also control antioxidant and anti-inflammatory cellular responses. Therefore, the modulation of this transcription factor can be a new therapeutic approach to reduce complications in chronic kidney disease (CKD) patients, like oxidative stress and inflammation, which leads to increased risk of developing cardiovascular disease, the major cause of death in these patients. Recent studies have shown that nutritional components and physical exercises can regulate the activation of Nrf2; however, very few studies were performed in CKD patients. This review provides an overview about some of the nonpharmacologic strategies that may promote the activation of Nrf2, which may have impact on the human health, particularly in CKD, by preventing oxidative stress and maintaining cellular redox homeostasis.

Introduction

CHRONIC KIDNEY DISEASE (CKD) patients are subjected to oxidative stress and inflammation, which results from an imbalance between reactive oxygen species (ROS) production and insufficient endogenous antioxidant defense mechanisms. These common findings are considered to play a critical role in the progression of CKD and related complications, mainly the increased risk of developing cardiovascular disease (CVD), which is the major cause of death in these patients, particularly for those on dialysis. CKD exacerbates by >20-fold the risk of death due to CVD, and *vice versa*, but the mechanisms and consequences of this interplay are not fully understood. Thus, mechanisms involved in the inactivation of oxidative stress and inflammation have been highlighted for being considered promising approaches to minimize cardiovascular complications.[1-3]

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a transcription factor that stimulates antioxidant synthesis. In fact, several studies showed that Nrf2 has emerged as a therapeutic target in many diseases, playing an important role in cellular protection against oxidative stress and inflammation.[4-8] Since recent studies show that children with premature aging (Hutchinson-Gilford progeria syndrome) have a repression of the Nrf2 antioxidant pathway[9] and exceptionally long-lived rats (naked mole rats) have higher expression of Nrf2 than ordinary mice,[10] it has been speculated that Nrf2 is a guardian of health span and longevity in different species.[11]

CKD patients seem to conserve regular homeostatic balance between the expressions of Nrf2 and nuclear factor-kB (NF-κB), which is involved in inflammatory response, being comparable with healthy individuals.[12] In contrast, hemodialysis (HD) patients have shown a downregulation of Nrf2 coupled to an upregulation of NF-κB expression.[13] Given the contribution of the impaired Nrf2 system in the pathogenesis of oxidative stress and inflammation, which play a central role in promoting CVD and related complications, therapeutic strategies aimed to restoring Nrf2 expression may be of benefit to CKD patients, mainly for those in dialysis treatment.

Several nutritional components have been shown to modulate Nrf2 expression, demonstrating the beneficial effects on this transcription factor.[14-21] Curiously, the importance of diet on the risk for cardiovascular complications was recently highlighted in a Chinese study of 451,665 participants which demonstrated that a higher level of fresh fruit consumption, lower blood pressure, and blood glucose levels ower risks of major CVD.[22] Furthermore, physical exercises are also able to activate Nrf2.[23-26] Nevertheless, few studies have assessed the effects of nonpharmacologic strategies on Nrf2 modulation in CKD patients. Therefore, this review aims to discuss some of nonpharmacologic strategies, like bioactive compounds and physical exercises, which can modulate the transcription factor Nrf2 in CKD.

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Nuclear Factor Erythroid 2–related Factor 2

Nrf2 is a transcription factor with a high sensitivity to oxidative stress, which regulates the expression of detoxifying enzymes controlling antioxidant and anti-inflammatory cellular responses.

Under basal conditions, Nrf2 binds to its cytosolic repressor, Kelch-like ECH-associated protein 1 (Keap1), which promotes its proteasomal degradation. However, in response to electrophiles, ROS, nitric oxide, oxidized low-density lipoproteins, prostaglandins, among others, Nrf2 dissociates from Keap1, possibly due to the interaction of certain cysteine residues within Keap1 molecules, which in turn modifies its conformation and blocks the proteasomal degradation of Nrf2. Nrf2 then translocates into the nucleus where interacts with small musculoaponeurotic fibrosarcoma and co-activator proteins, that allow its binding to the antioxidant response elements in their promoter regions, activating its target gene transcription.[5,6,8,27-29]

Nfr2 plays a central role in basal activity and coordinated induction of more than 250 genes, including those encoding phase II detoxifying and antioxidant enzymes: heme oxygenase-1, (HO-1), nicotinamide adenine dinucleotide phosphate (NAD(P)H), quinone oxidoreductase 1 (NQO-1), glutathione S-transferase (GSTs), glutathione peroxidase (GPx), glutamate cysteine ligase, catalase (CAT), superoxide dismutase (SOD), uridine 5'-diphospho-glucuronosyltransferase, thioredoxin, peroxiredoxins, and others. These enzymes are essential to remove ROS and other toxic products and, thus, Nrf2 plays a crucial role in cellular defense against oxidative stress.[6,8,13]

Oxidative stress and inflammation are inseparably linked and work as partners in crime as they form a vicious cycle[30] in which ROS provokes inflammation by several mechanisms including activation of NF-κB. Inflammation, in turn, causes oxidative stress through the production of ROS.[31] Besides acting in cellular defense against oxidative stress, Nrf2 is also a key transcription factor involved in cytoprotection against inflammation, which has been related to its ability to antagonize NF-κB (through preventing the degradation of its cytosolic repressoror, IκB), a factor that regulates the transcription of several genes encoding proinflammatory cytokines, chemokines, and leukocyte adhesion molecules.[31,32]

Because activation of Nrf2 results in the concerted upregulation of several antioxidant enzymes and cytoprotective genes, it has been regarded as an attractive target for many different disease including CKD and diabetes. In fact, Nrf2 can be regarded as a "multiorgan protector" because it protects many cell types and organ systems from a broad spectrum of toxic insults and several diseases. However, too much activation of Nrf2 may also to be detrimental. Indeed, Keap1 knockout mice die within a couple of weeks after birth,[33] and there have been reports that increased Nrf2 activation promotes cancer resistance.[34] We also learned from the bardoxolone trial that Nrf2 activation increased the risk of cardiovascular side effects in CKD patients. [35] Because it was recently demonstrated that an Nfr2 inducer has dose-dependent deleterious and salutary actions,[36] we need to learn more about the window within NrF2 activators offers effective protection.

Although there are not many studies evaluating Nrf2 messenger RNA expression in CKD, some studies have shown an altered Nrf2 expression. In fact, reduced Nrf2 activity was found in nephrectomized rats, pointing to its role as a common mediator in the pathogenesis and progression of CKD, independent of the underlying etiologies.[31,37,38] In HD patients, our research group has shown a downregulation of Nrf2 and upregulation of NF-κB in the peripheral blood mononuclear cells.[13] These findings show an impaired Nrf2 pathway in the pathogenesis of oxidative stress and inflammation, in humans and experimental animals with CKD. However, the mechanism by which CKD cause Nrf2 deficiency and dysfunction is still unclear. A possible candidate is systemic inflammation, a common finding in the uremic phenotype. This hypothesis is based on the observation that the active subunits of NF-κB, that is, P65 and P53, can interfere with the dissociation of Nrf2 from its cytosolic repressor, Keap1, and consequently with Nrf2 binding to the antioxidant response elements of the target genes in the cell nucleus.[39,40]

Therefore, therapeutic strategies like nutritional components and physical exercises aimed to restoring Nrf2 expression may be beneficial in CKD.

Nutritional Components and Nrf2 Modulation in CKD

The positive relationship between Nrf2 and CKD protection has attracted much interest, leading researchers to make an effort to use Nrf2 activators as a novel therapeutic strategy in CKD. In particular, there have been extensive investigations on naturally occurring compounds that promote the activation of Nrf2, which may have impact on the human health, and thus, are able to prevent oxidative stress and maintain cellular redox homeostasis. Several authors revealed Nrf2 modulation by bioactive compounds present in food, such as garlic,[14] ginger,[15] purple sweet potato,[16] coffee,[17] pomegranate,[18] berries and walnuts,[19] fish oil,[20] soy[21] among others. Studies suggest that doses found in whole foods and food combinations may have more beneficial effects than specific bioactive compounds in supplements at supraphysiological doses.[41]

Here, we discuss current findings of the role of Nrf2 activation by resveratrol, curcumin, catechins, sulforaphane (SFN), oleanolic acid, sesame oil, resistant starch, cinnamaldehyde (CA), lycopene, and selenium (Se), with a particular emphasis on CKD.