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Emerging Roles of Nuclear Factor Erythroid 2 Related Factor 2 in Podocytopathy: a Review

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Abstract

Podocytopathy is characterized as the clinical manifestation of massive proteinuria and the changes in morphology and quantity of podocytes, which is attributed to podocyte injury or dysfunction and subsequently leads to renal failure. Since effective therapeutic strategies are still limited, to find new methods for treatment of this disease is important. Oxidative stress has been found to involve in the initiation and progression of podocytopathy. Additionally, nuclear factor erythroid 2 related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1)-antioxidant-responsive element (ARE) system plays a key role in the cell's response to oxidative stress. Therefore, activation of Nrf2 seems to be a potentially effective method for the treatment of podocytopathy. In this paper, we will summarize the information available regarding the effect of Nrf2 on podocytopathy, especially through Nrf2/Keap1-ARE pathway.

Keywords: Nuclear factor erythroid 2 related factor 2; Oxidative stress; Podocytopathy

Introduction

Podocyte is a kind of epithelial cell with interdigitating foot processes separated by a slit diaphragm. Previously, it was difficult to study podocyte *in vivo* due to its special anatomy. Moreover, primary podocyte from normal adult human kidney couldn't passage owning to its terminally differentiated property, therefore, the research work studying podocyte *in vitro* was also limited.

Until the end of 1990s, the establishment of the immortalized cell line highlighted the understanding of the podocyte structure and the underling mechanism in glomerular disease [1]. As renal capsule visceral epithelial cells, podocytes enwraps the outside of the glomerular basement membrane (GBM). Podocytes, together with the GBM and capillary endothelial cells constitute the glomerular filtration barrier to regulate the passage of proteins from capillary lumen to Bowman's space [2]. And besides, this terminally differentiated cell also plays a battery of physiological functions including: remodelling the GBM [3,4] and endothelial cells [5,6], provision of structural support for the glomerular capillary, regulating mesangial cell migration and survival [7] as well as endocytosis of filtered proteins [8].

Podocytopathy is the group of glomerular diseases, characterized as the clinical manifestation of massive proteinuria and the changes in morphology and quantity of podocytes under electron microscope, which is attributed to podocyte injury or dysfunction [9]. It is now recognized that minimal change disease [10], focal segmental glomerulosclerosis (FSGS) [11], idiopathic membranous glomerulopathy [12], crescentic glomerulonephritis [13], collapsing glomerulopathy [14], diabetic nephropathy [15], obesity-related glomerulopathy [16] and lupus nephritis [17] share the common features-podocyte damage and dysfunction. It was a major switch in our understanding of the pathophysiology and pathology of glomerular diseases because of the conception of podocytopathy, which was the early-stage event. The realization that glomerular diseases could be reversed by focusing on this early-stage event has led to the current theory that novel therapeutics should inhibit podocyte damage and dysfunction.

The mechanisms of podocyte diseases are complicated. The most studied is the skeleton protein [18,19], followed by gene mutation [20], as well as TGF-β dependent [21]. In recent years, the role of oxidative stress in podocyte injury is gradually being concerned [22,23]. Moreover, nuclear factor erythroid 2 related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1)-antioxidant-responsive element (ARE) system plays a key role in the cell's response to oxidative stress [24-26]. Therefore, activation of Nrf2 seems to be a potentially effective method for the treatment of podocytopathy. Here, we seek to review the contribution of Nrf2/Keap1-ARE system to podocytopathy.

Oxidative Stress and Podocytopathy

Our body is under persistent oxidative attack from reactive oxygen species (ROS), and a complex antioxidant defence system has evolved that normally keeps this attack in balance [27]. Oxidative stress and reductive stress are dual dynamic phases

experienced by the cells undergoing adaptation towards both endogenous and exogenous noxious stimulus. Oxidative stress is defined by the imbalance between the production of ROS and the endogenous antioxidant mechanisms. Under physiological condition, several precisely controlled oxidative pathways contribute to ROS generation, while several endogenous antioxidant enzymes account for ROS purge [28]. Both reduced ROS detoxification and increased ROS generation can lead to cellular macromolecules damage, including DNA oxidation [29], lipid peroxidation [30] and protein modification [31]. These damages, if left unrepaired, can cause mutations which lead to diseases.

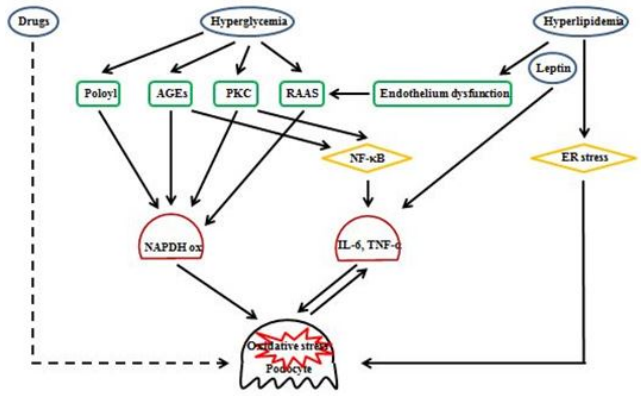

Figure 1: Described pathways under which oxidative stress occurred in podocytopathies for different kidney diseases. AGEs: Advanced Glycation End products; ER stress: Endoplasmic Reticulum Stress; IL-6: Interleukin 6; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NF-κB: Nuclear Factor Kappa B; PKC: Protein Kinase C; RAAS: Renin Angiotensin-aldosterone System; TNF-α: Tumor Necrosis Factor Alpha.

Podocyte injury, a major contributor to the proteinuric glomerular diseases, is caused at least in part by the excessive generation of ROS [32,33]. Considerable evidences show that ROS involved in podocyte injury in a variety of disease states, such as diabetes [34-36], hyperlipidaemia [22], FSGS [37], renal ischemia-reperfusion [23], together with drug-induced kidney damage [38,39]. For example, under hyperglycaemia condition, activation of polyol pathway, protein kinase C signalling pathway and renin angiotensin-aldosterone system, as well as the generation of advanced glycation end products tend to increase oxidative stress by inducing the action of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.

In addition, under obese condition, hyperlipidaemia-induced activation of renin angiotensin-aldosterone system and excessive ER stress together with hyperleptinimia-induced inflammation result in oxidative stress. Moreover, certain drugs can lead to oxidative stress through a particular mechanism. Described pathways under which oxidative stress occurred in podocytopathies for different kidney diseases were shown in (**Figure 1**). Therefore, against oxidative stress or reduce ROS production can become a new method to treat podocytopathy.

NRF2/KEAP1-are Signalling Pathway and Oxidative Stress

The basic leucine zipper transcription factor family member, Nrf2, is the central of antioxidant system and plays an important role in cellular resistance to oxidative stress [40]. Nrf2/Keap1-ARE signalling pathway is regulated by complex mechanisms. Under normal conditions, Nrf2 exists in cytoplasm as its inactive form. Keap1, works as an inhibitor, binds tightly to Nrf2 to anchor this transcription factor in the cytoplasm [41]. Keap1 also serves as a mediator that ultimately leads to ubiquitination and proteasomal degradation of Nrf2, thereby the ability of Nrf2 to induce phase II detoxification enzyme genes is repressed [42]. Under abnormal conditions, such as exposure to oxidative stress and certain antioxidants, the Nrf2/Keap1 complex structure will be changed by modifying two (Cys273 and Cys288) of the 25 cysteine residues of Keap1 [43], leading to the cytoplasmic-to-nuclear translocation of Nrf2. In the nucleus, Nrf2 up-regulates gene expression of phase II detoxifying and/or antioxidant enzymes [44,45] by binding ARE or electrophile response element, which locates at the 5-flanking region of the phase II detoxification enzyme genes [46].

Promotion of Nrf2 cytoplasmic-to-nuclear translocation, modification of the Nrf2/Keap1 complex and inhibition of Nrf2 degradation are important to Nrf2/Keap1-ARE pathway dependent gene expression, and several signalling pathways are associated with these processes. Our previous study revealed that Zinc maintains Nrf2 normal expression and transcription function through Akt/GSK-3β-mediated inhibition of Nrf2 nuclear exporter Fyn [47]. In HepG2 cells, Huang et al. found that PKC could promote Nrf2 phosphorylation at Ser-40, which remoulded the Nrf2/Keap1 complex and lead to the dissociation of Nrf2 from Keap1 [48].

In another study from our group, we found that MG132 up-regulated Nrf2 function *via* inhibiting the increased proteasomal activity in diabetic mouse model [49]. Taken together, whether up-regulating Nrf2/Keap1-ARE signalling pathway directly by promotion of Nrf2 cytoplasmic-to-nuclear translocation and modification of the Nrf2/Keap1 complex or indirectly by inhibition of Nrf2 degradation, provides a valuable tool for the treatment of oxidative stress-associated injury.

Diabetic Nephropathy

Podocyte injury caused by oxidative stress contributes to onset and progression of diabetic nephropathy and related functional deficits like albuminuria and decreased glomerular filtration rate [50]. Therefore, diminishing oxidative stress exerts podocyte-protective effects in diabetic nephropathy. Cao et al. used ursodeoxycholic acid to treat podocytes under high glucose condition, and found that ursodeoxycholic acid treatment alleviated high glucose induced ROS generation in podocytes [51].

To explore whether activation of Nrf2/Keap1-ARE pathway attenuated high glucose induced podocyte injury, both Nrf2 inducer and Nrf2 siRNA were used to regulate Nrf2 expression in mouse podocytes [52]. In this *in vitro* study, Wang et al. found

that up-regulation of Nrf2 and its downstream genes decreased high glucose induced intracellular ROS production, apoptosis rate and bovine serum albumin permeability, while Nrf2 siRNA treatment aggravated these injuries, indicating that activation of Nrf2/Keap1-ARE pathway could be a therapeutic option to combat oxidative stress and inhibit the development of diabetic nephropathy [52].

The therapeutic effects of Nrf2/Keap1-ARE pathway activation on podocytes in diabetic nephropathy were also proved in an *in vivo* study. Improved albuminuria, renal interstitial inflammation and glomerular sclerosis were found after a single dose of lectin-like domain of thrombomodulin injection in db/db mice and these effects were partially associated with promotion of Nrf2 nuclear translocation [53]. Taken together, available evidence supports the beneficial roles of Nrf2/Keap1-ARE pathway activation in the treatment of diabetes-induced podocyte injury.

FSGS

FSGS clinically features heavy proteinuria or nephrotic syndrome and defined by characteristic lesions of focal glomerular sclerosis and podocyte foot process effacement [54]. It has been proved that oxidative stress was involved in the pathogenesis of this podocytopathy [55].

The therapeutic effects of activation of Nrf2/Keap1-ARE pathway on alleviating podocyte injury and renal damage in FSGS mice were evaluated by a series of studies from one Chinese group [56-58]. In these studies, the FSGS mouse model was introduced by intravenously injection of a single dose of adriamycin in 8-week-old female BALB/c mice and then antroquinonol [56], citral [57] or osthole [58] were administrated, respectively. At the indicated time course, markers of renal function, podocyte injury, oxidative stress, as well as Nrf2/Keap1-ARE pathway were detected.

These results demonstrated that all these compounds can (1) attenuate proteinuria, renal dysfunction and podocyte injury; (2) reduce oxidative stress; (3) activate renal Nrf2/Keap1-ARE pathway [56-58]. However, whether these renal protective effects were Nrf2/Keap1-ARE pathway dependent was not addressed in the above studies. Therefore, Nrf2 activator and Nrf2 knock mice are helpful to make sure this issue in further study.

Crescentic Glomerulonephritis

Crescentic rapidly progressive glomerulonephritis is a severe syndrome characterized by a rapid loss of renal function as well as podocyte injury. To explore the therapeutic potential of Nrf2-peroxisome proliferator-activated receptor gamma (PPARγ) pathway in treating crescentic glomerulonephritis, Henique et al. found that podocyte-specific *Pparγ* gene targeting lead to increased urinary protein and severe renal failure. Meanwhile, activation of PPARγ by thiazolidinedione administration failed to prevent the severe damage in podocyte-specific Pparγ gene deficiency mice. Moreover, in Nrf2 knockout mice, loss of podocyte PPARγ and aggravated the course of rapidly progressive glomerulonephritis were observed, which could be partially prevented by thiazolidinedione administration [59]. This study provides the evidence that the Nrf2-PPARγ pathway may be a therapeutic target for crescentic rapidly progressive glomerulonephritis.

It is worth noting that, the efficacy of Nrf2/Keap1-ARE pathway activation in crescentic glomerulonephritis has been proved [60]. However, whether Nrf2/Keap1-ARE pathway takes part in the protection of crescentic glomerulonephritis remains unknown.

Obesity-related Glomerulapathy

Obesity, recognized as a major feature of metabolic syndrome, has become a big social problem worldwide. A large number of studies demonstrate that ROS plays an important role in regulation of glucose and lipid metabolism [61]. The role of the Nrf2/Keap1 pathway in obesity and metabolic syndrome was well reviewed by Zhang et al. [62]. The effects of regulating oxidative stress by Nrf2 on phenotypes of obesity were complex. With deletion of the *Nrf2* gene, increased oxidative stress and ROS generation in obesity was expected to deteriorate the obesity phenotypes [63]. However, a series of studies showed that deletion of the *Nrf2* gene in mice ameliorated the obesity phenotypes, including insulin resistance, hyperglycaemia, hyperlipidaemia and overweight [64,65]. These contradictory results of Nrf2 on obesity are possibly due to the difference in ROS flux levels in different animal models, such as high fat diet-induced obese mice, db/db mice and ob/ob mice.

Interestingly, consistent results were found in experiments using Nrf2 pharmacological activators. All these specific Nrf2 activators significantly improved glucose intolerance and attenuated insulin resistance [66-70]. One possible reason interprets the difference between studies using Nrf2 activators and Nrf2 deficiency mice might be Nrf2 activators and Nrf2 deficiency work through distinct mechanisms. Unfortunately, no study observes the effects of Nrf2/Keap1-ARE pathway on obesity-induced kidney damage and podocyte injury.

Others

The protective effect of Nrf2 on podocytopathy was also found in other experiment model. In study from Zhou et al., primary podocyte and doxycycline-inducible podocyte-specific glycogen synthase kinase 3β gene knockout mice were used and treated with doxorubicin [71].

This study revealed that both genetic and pharmacologic targeting of glycogen synthase kinase 3β alleviated doxorubicin-induced podocyte injury by reinforces the Nrf2 antioxidant defence [71]. Detail information from the articles studying the effects of Nrf2/Keap1-ARE signalling pathway on podocytopathy was listed in (**Table 1**).

Table 1: Effects of Nrf2/Keap1-ARE signalling pathway on podocytopathy.

Disease model	Intervention medicine	Nrf2 knockout	Reference
Diabetic Nephropathy			
Podocyte, high glucose stimulation	Tert-Butylhydroquinone	Yes	[52]
db/db mice	Lectin-like domain of thrombomodulin	No	[53]
Focal segmental glomerulosclerosis			
Adriamycin-induced focal segmental glomerulosclerosis mice	Antroquinonol	No	[56]
Adriamycin-induced focal segmental glomerulosclerosis mice	Citral	No	[57]
Adriamycin-induced focal segmental glomerulosclerosis mice	Osthole	No	[58]
Crescentic glomerulonephritis			
Sheep anti-mouse GBM nephrotoxic serum-induced crescentic glomerulonephritis mice	Thiazolidinedione	Yes	[59]
Others			
Primary podocytes and mice, doxorubicin stimulation	SB216763	No	[71]

Conclusions

In summary, oxidative stress involves the pathogenesis of podocytopathy. As the central of body antioxidant system, Nrf2, epically Nrf2/Keap1-ARE pathway plays an important role in podocytopathy treatment. This review provides evidence for future clinical research studying the therapeutic potential for the treatment of podocytopathy.

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Conflicts Of Interest

None declared.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Author's Contribution

WC and LM designed this manuscript; WC and YC wrote this manuscript; YW and ML searched the articles. All of the authors read and approved the final manuscript.

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