

Mini-review

Evaluating the Ubiquitin–proteasome System as a Therapeutic Target in Diabetic Kidney Disease

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Received: June 05, 2018; **Accepted:** July 30, 2018; **Published:** August 05, 2018

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Abstract

Diabetic kidney disease (DKD) is a major health problem, and its prevalence has been increasing worldwide. Therefore, there is an urgent need to identify a new therapeutic target to prevent DKD. Regardless of the presence of diabetes mellitus, the final common pathway in chronic kidney disease is oxidative stress. Therefore, oxidative stress pathway molecules are appropriate targets for therapies against DKD. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a master transcription factor for antioxidant and detoxification responses. Bardoxolone methyl, an inducer of the Nrf2 pathway protects against oxidative stress and can even reverse impaired renal function. Nrf2 is degraded by the ubiquitin-proteasome pathway. Previous studies have demonstrated that proteasome inhibition can upregulate expression of Nrf2 protein to protect cells from oxidative damage. In this review, we discuss the association between the pathogenesis of DKD and the ubiquitin–proteasome system (UPS). Diverse roles of the UPS are implicated in the development of kidney diseases, and further studies on this system may reveal new strategies for overcoming kidney diseases.

Keywords: Diabetic kidney disease (DKD), proteasome, oxidative stress, Nrf2

Introduction

Kidney disease progresses through the common pathway and leads to end stage renal failure. Treatment targeting this common pathway is a common treatment for various kidney diseases. Oxidative stress plays an important role in various kidney diseases. A meta-analysis revealed that antioxidant therapy in kidney disease is effective [1]. However, vitamin C, vitamin E, etc., have been mainly used as antioxidants in clinical trials. Although the antioxidant action of angiotensin receptor antagonists is also gaining attention, it is desirable to produce and apply this compound as an antioxidant in clinical trials.

It has been shown that the proteasome plays a crucial role in several organs, especially in metabolic organs and that its alteration is involved in the pathogenesis of metabolic [2,3] and age-related diseases [4-6]. Based on these findings, it is not surprising that abnormalities in the proteasome system are also associated with the pathogenesis of DKD. Interestingly, proteasomal activity decreases in the diabetic mouse or rat kidney [7,8], while the $\alpha 6$ subunit of the 20S proteasome decreases in the diabetic rat kidney [9], and high glucose decreases the $\beta 6$ subunit of the 20S proteasome in mesangial cells [10]. The functional role of the proteasome in the kidneys is currently under intense

investigation, and it has been shown that the proteasome has a critical role in several animal models, including those used for acute kidney injury [11-13]. In this review, we mainly discuss protein degradation via the ubiquitin–proteasome system (UPS), which is the pathway used for the specific and selective proteolysis of intracellular proteins and discuss its relationship to the pathogenesis of kidney diseases.

Pathways for protein degradation

In mammalian tissues, protein degradation involves three main pathways: the ubiquitin–proteasome, lysosomal, and the Ca²⁺-dependent systems. Protein degradation via the ubiquitin–proteasome system (UPS) is the major pathway for the non-lysosomal proteolysis of intracellular proteins and plays important roles in a variety of fundamental cellular processes, such as the regulation of cell cycle progression, differentiation, apoptosis, the sodium channel function, and modulation of inflammatory responses. The central element of this system is the covalent linkage of ubiquitin molecules to targeted proteins, which are then recognized by the 26S proteasome composed of adenosine triphosphate-dependent multi-catalytic proteases [14]. Damaged or misfolded proteins, as well as regulatory proteins that control many critical cellular functions, are among the targets of this degradation process. Consequently, dysfunction of the system leads to the dysregulation of cellular homeostasis and the development of many diseases.

Oxidative stress

Oxidative stress has been suggested to be involved in the development and progression of DKD [15-17]. As the central cause of oxidative stress, overproduction of reactive oxygen species (ROS) can cause cellular abnormalities, by reacting directly with nitric oxide to produce cytotoxic peroxynitrite and thus increasing reactivity to vasoconstrictors, and modifying extracellular matrix proteins [18,19]. ROS also damage cells indirectly by stimulating the expression of transcriptional factors involved in inflammatory pathways, such as NF- κ B [20]. The NADPH oxidase is a major source of ROS production and may be a key player in the regulation of cellular redox reactions [21,22]. The processes for oxidative stress include the increased generation and decreased elimination of ROS that could be caused by an impaired antioxidant defense system.

Nuclear factor (erythroid-derived 2)-like (Nrf2)

The transcription factor Nrf2 is confined to the cytoplasm as an inactive complex bound to a repressor molecule called Kelch-like ECH-associated protein 1 (Keap1), which facilitates ubiquitination of Nrf2. Previous studies have demonstrated that proteasome inhibition can upregulate expression of Nrf2 protein to protect cells from oxidative damage [23,24]. Under physiological conditions, Nrf2 is bound to its inhibitor Keap1, which mediates the rapid ubiquitination and subsequent degradation of Nrf2 by the proteasome [25]. Generally, and in response to high ROS production, Nrf2 is freed from Keap1 and translocates to the nucleus to bind to antioxidant-responsive elements (ARE) in the genes encoding antioxidant enzymes, such as superoxide dismutase 1 (SOD1), catalase (CAT), glutathione peroxidase (GPx), heme oxygenase 1 (HO-1), and GSH S-transferase (GST), thus increasing their expression [26].

Yoh et al. [27] showed that hyperglycemia increased oxidative and nitrosative stress and accelerated renal injury in Nrf2 knockout mice and that Nrf2 serves as a defense factor against some diabetic complications.

Bardoxolone methyl (also known as “RTA 402” and “CDDO-methyl ester”), which can suppress oxidative stress and inflammation, is an inducer of the Nrf2 pathway. A phase 2 multi-center RCT (BEAM) study in patients with moderate to severe chronic kidney disease (CKD) and type 2 diabetes reported that eGFR was increased (>10 ml/min/1.73 m²) in patients treated with bardoxolone methyl for 24 months [28]. An analysis of secondary endpoints showed that approximately three-quarters of bardoxolone methyl-treated patients experienced at least a 10 percent

increase in eGFR, and one-quarter of the patients had an improvement of 50%. Bardoxolone methyl was expected to be the first in class drug for the treatment of DKD. The occurrence of renal events (BEACON) trial study was designed to establish whether bardoxolone methyl slows or prevents progression towards end-stage renal disease (ESRD) [29]. Among patients with type 2 diabetes mellitus and stage 4 CKD, bardoxolone methyl did not reduce the risk of ESRD or death from cardiovascular causes. A higher rate of cardiovascular events occurring with bardoxolone methyl treatment than with the placebo prompted the termination of the trial. We hope for the development of other therapeutic approaches that target Nrf2 in DKD patients.

The effects of proteasome inhibition on the expression of Nrf2

Previously, Luo et al. [30] showed that a treatment with a low-dose of MG132, a proteasome inhibitor, can act as a new intervention therapy that can effectively inhibit oxidative stress and the related inflammatory response of the kidneys. They also showed that this provides renoprotection in diabetes-induced rats suffering from nephropathy via the chronic, nontoxic proteasome inhibition (Figure 1). Therapeutic approaches to prevent oxidative stress via the activation of the Nrf2-Keap1 signaling pathway could be effective strategies for maintaining kidney function. Although the precise details should be explored in future studies, these studies provide a theoretical basis for further studying the clinical prevention and treatment of DKD via proteasome inhibition.

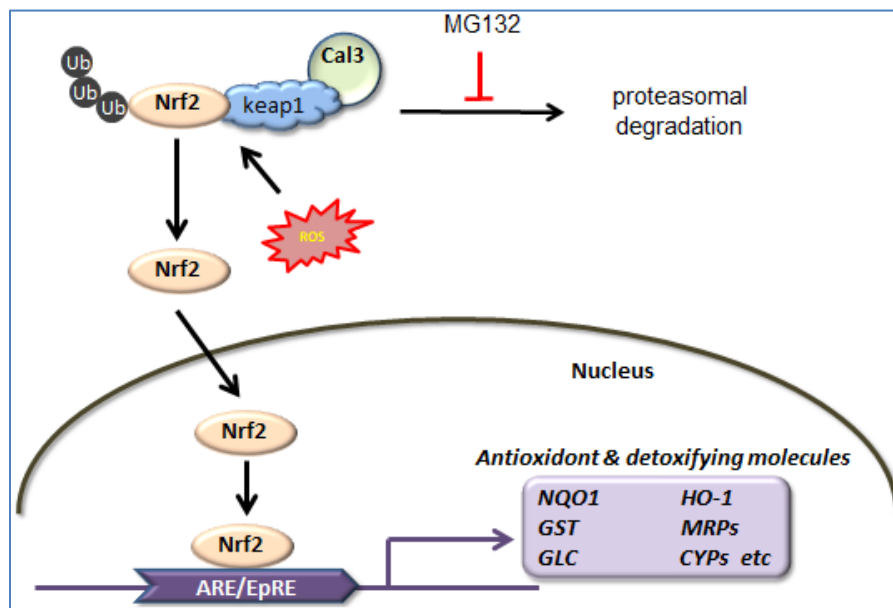


Figure 1: Effect of MG132 on renal Nrf2 activation. MG132 upregulates the expression of Nrf2 protein to protect cells from oxidative stress

Conclusions

In recent decades, numerous investigators have made efforts to identify the molecular mechanisms involved in the initiation and progression of DKD, in order to develop new therapeutic strategies. However, end-stage renal disease, due to DKD, continues to increase worldwide. There is an urgent need to identify additional new therapeutic targets for the prevention of DKD. We have provided a perspective on whether UPS is involved in the pathogenesis of DKD, and whether it is an acceptable new therapeutic target. Unfortunately, there have not been many studies published that have focused on UPS in DKD. Finally, future studies will ultimately give us a clearer perspective as to whether UPS should be considered as a novel therapeutic target to halt the progression of DKD.

Conflict of Interests

The authors declare that there is no conflict of interest.

Acknowledgments

This work was partially supported by grants from the Japan Society for the Promotion of Science awarded to Toshiki Otoda (18K16204).

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