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REVIEW

MG53: A potential therapeutic target for kidney disease

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Abstract

Ensuring cell survival and tissue regeneration by maintaining cellular integrity is important to the pathophysiology of many human diseases, including kidney disease. Mitsugumin 53 (MG53) is a member of the tripartite motif-containing (TRIM) protein family that plays an essential role in repairing cell membrane injury and improving tissue regeneration. In recent years, an increasing number of studies have demonstrated that MG53 plays a renoprotective role in kidney diseases. Moreover, with the beneficial effects of the recombinant human MG53 (rhMG53) protein in the treatment of kidney diseases in different animal models, rhMG53 shows significant therapeutic potential in kidney disease. In this review, we elucidate the role of MG53 and its molecular mechanism in kidney disease to provide new approaches to the treatment of kidney disease.

KEYWORDS
acute kidney injury, clinical application, kidney fibrosis, membrane repair, MG53

1 | INTRODUCTION

Kidney dysfunction, which can be classified as acute kidney injury (AKI) or chronic kidney disease (CKD), has grown into an epidemic worldwide. AKI is a common disease with high morbidity and mortality that is characterized by the rapid loss of renal function. The importance of some negative regulators of inflammation remains unclear with respect to the long-term outcome following chronic postischemic AKI.[1] Long-term cohort studies have suggested that AKI is an underestimated yet significant risk factor for CKD,[1] particularly for contrast-induced (CI) nephrotoxicity,[2] cardiothoracic surgery,[3] and nephrotoxic chemotherapy.[4] The pathological changes in CKD mainly manifest as kidney fibrosis. This is a complicated process characterized by increased fibroblast proliferation and the accumulation of extracellular matrix (ECM), leading to renal tubule fibrosis, glomerulosclerosis, renal artery stenosis, and chronic inflammatory cell infiltration.[5] Recently, new strategies, such as inhibitors of sodium-glucose cotransporter 2 (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP1-RA), have been reported to alleviate kidney disease progression[6,7]; however, SGLT2i and GPL1-RA are contraindicated in patients with severe renal insufficiency. Unfortunately, treatments to attenuate kidney disease are limited.

MG53 is a member of the tripartite motif-containing (TRIM) protein family that can be secreted from the muscle into the blood circulation. It participates in multiple physiological and pathological processes, including wound healing, the suppression of cell apoptosis, decreased oxidative stress, the inhibition of the inflammatory response, the inhibition of aberrant intracellular Ca^{2+} signaling, and insulin resistance.[8–12] Moreover, MG53 is involved in the regulation of many human diseases, including cardiac diseases,[13] lung cancer,[14]

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; MG53, Mitsugumin 53; rhMG53, MG53; TRIM, tripartite motif-containing.

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diabetes mellitus,[15] and muscular dystrophy.[16] Generally, MG53 plays an essential role in repairing cell membrane injury and improving tissue regeneration.[17,18] Within a lifetime, cells may be injured by different factors. If the membrane damage is not repaired in a timely manner, the injury can cause cell death and permanent tissue damage. It is critical to ensure cell survival and tissue regeneration by maintaining cellular integrity, since defects in cell membrane repair are related to the pathophysiology of many human diseases.[18] Cell membrane injury, especially proximal tubular epithelial cells (PTECs), plays an active role in AKI and CKD.[19,20] Studies have shown that MG53 is expressed at low levels in the inner cortex of the kidney.[21] Moreover, when PTECs are damaged, MG53 translocates from the serum to the injury sites to protect PTECs.[20] In addition, since recombinant human MG53 (rhMG53) protein is an attractive biological reagent for the restoration of membrane repair defects,[22] rhMG53 shows significant therapeutic potential for kidney disease[19,23] (Table 1). Therefore, we clarify the role of MG53 and its molecular mechanism in kidney disease in this review to provide new opportunities for the treatment of kidney disease.

2 | MG53 AND AKI

AKI is a disease with a high mortality rate that is encountered in hospital and outpatient settings. Currently, there are no effective cures for preventing or treating AKI. This leads to lengthy hospital stays for patients who develop AKI, incurring great costs for the treatment of AKI and the prevention of progression to chronic kidney failure.[23] Renal PTEC injury is the most common cause of AKI, and delayed recovery from tubular epithelial injury can lead to irreversible renal injury, causing CKD.[24,25] Thus, accelerating the recovery of damaged PTECs is of great importance in the treatment of AKI.

MG53 translocates to the injury site and binds to phosphatidylserine (PS) to mediate a membrane protective effect on PTECs in AKI (Figure 1). A study demonstrated that MG53 deficiency increases myocardial vulnerability to ischemia/reperfusion (I/R) injury.[26] A study showed that the deletion of MG53 was linked to defective membrane repair in PTECs.[23] MG53-deficient mice develop severe tubulointerstitial damage and increased susceptibility to I/R-induced AKI.[23] MG53 mediates membrane repair in a cholesterol-dependent manner.[27] Due to its low expression in the kidney, MG53 can translocate to acute injury sites via PTECs in the serum.[20,23] When cells are damaged, cholesterol is exposed on the cell membranes. PS, a phospholipid, is usually sequestered in the inner leaflet of the plasma membrane but may be exposed to the extracellular environment.[4] When PTECs are injured by CI, I/R, cisplatin and cardiothoracic surgery, MG53 can bind to PS at the injury site to reduce cell membrane damage and apoptosis by providing an anchoring mechanism for the tissue-protective effect of MG53.[20,23]

3 | MG53 AND KIDNEY FIBROSIS

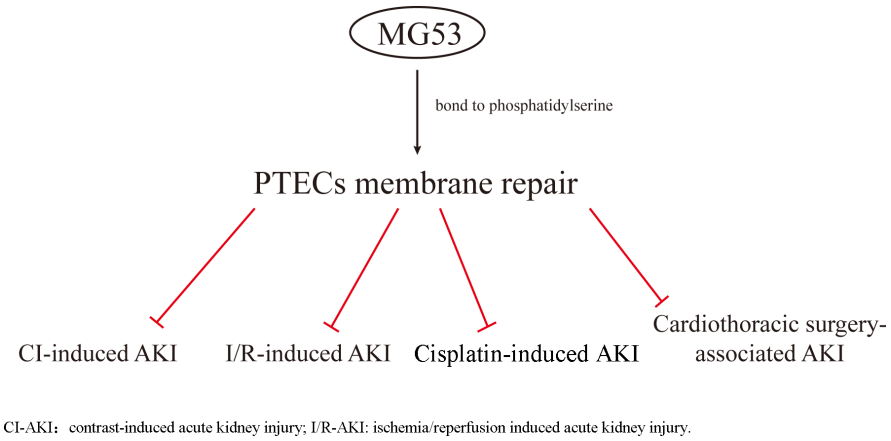
CKD has been recognized as a severe health problem globally. The estimated prevalence of CKD is between 8% and 16% worldwide.[28] In recent decades, significant progress has been made in understanding the mechanisms of CKD around the globe.[29] The major pathological change in CKD mainly manifests as kidney fibrosis. Generally, the mechanism underlying renal fibrosis development is related to the activation of transforming growth factor-beta (TGF-β) signaling, oxidative stress,[5] the activation of nuclear factor kappa B (NF-κB),[30] and pathological angiogenesis.[31] Thus, it is urgent to find means that can be used to effectively prevent and treat kidney fibrosis.

MG53 may play a renoprotective role in kidney fibrosis through a negative feedback loop between MG53 and TGF-β1 (Figure 2). Zhang et al. demonstrated that the depletion of MG53 reduced the expression of TGF-β1 and cell proliferation and migration in rat cardiac fibroblasts.[32] Jingwen Guo et al. also found that after the depletion of MG53, atrial fibroblasts showed lower expression levels of TGF-β1, and the migration and proliferation of fibroblasts was reduced. Moreover, the overexpression of MG53 upregulated the synthesis of TGF-β1.[33] In addition, Meixia Zhang et al. revealed that caveolin-1 (CAV1), an important antifibrosis signaling mediator that inhibits the TGF-β1 signaling pathway, is critical for MG53 regulation of the TGF-β1 signaling pathway.[34] These results indicate that MG53, as an upstream target of TGF-β1, positively regulates the TGF-β1 pathway by inhibiting CAV1. Furthermore, Jingwen Guo et al. revealed that rhTGF-β1 significantly suppressed the expression of MG53.[33] Li et al. showed that rhMG53 suppressed the upregulation of the TGF-β1/Smad pathway after

TABLE 1 Studies on the role of MG53 in the kidneys of different animal models

PMID	Authors	Animal model	RhMG53 doses	Mechanism
32424239	Chao Liu et al.	CI-AKI	2 mg/kg	bind with PS at the injury site to reduce cell membrane damage
25787762	Pu Duann et al.	I/R-AKI Cisplatin-induced AKI	2 mg/kg	
34757120	Haichang Li et al.	UUO mouse model	2 mg/kg	Inhibition of NF-κB signaling
30614598	Gu Lijie et al.	CKD rat model	None	Restore mitochondrial autophagy

Abbreviations: CI-AKI, contrast-induced acute kidney injury; I/R-AKI, ischemia/reperfusion-induced acute kidney injury; UUO, unilateral ureteral obstruction.



CI-AKI: contrast-induced acute kidney injury; I/R-AKI: ischemia/reperfusion induced acute kidney injury.

FIGURE 1 MG53 protects against multiple AKIs by facilitating PTEC membrane repair by binding to phosphatidylserine.

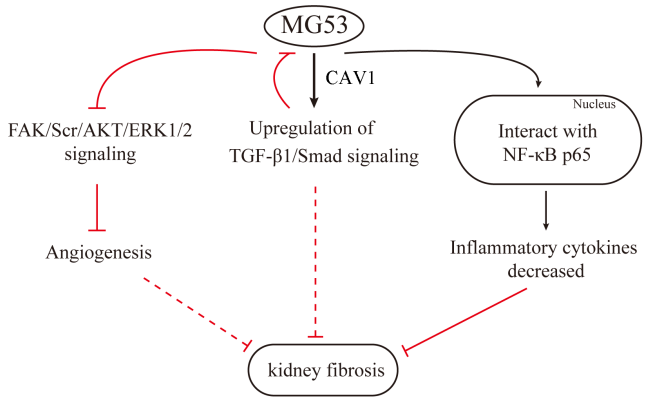


FIGURE 2 MG53 may attenuate kidney fibrosis by inhibiting FAK/Scr/AKT/ERK1/2 signaling, activating a negative feedback loop between MG53 and TGF-β1, and interacting with NF-κB p65 to decrease inflammatory cytokines.

treatment with exogenous TGF-β1 in three T3 cells.[35] All of the data suggest that TGF-β1 may have a negative feedback effect on MG53. However, the relationship between MG53 and TGF-β1 in kidney disease is poorly understood.

MG53 attenuates kidney fibrosis by directly interacting with the p65 component of the transcription factor NF-κB and reducing NF-κB activation and inflammation (Figure 2). A recent study showed that mice with ablation of MG53 develop age-related kidney fibrosis, which is related to increased expression of fibronectin and kidney infiltration by leukocytes and macrophages.[19] Furthermore, they found that the phosphorylation level of p65, a hallmark of NF-κB activation, was significantly increased in unilateral ureteral obstruction (UUO) kidneys from *mg53*$^{-/-}$ mice. Finally, they demonstrated that MG53 inhibits kidney fibrosis by preventing NF-κB p65 nuclear translocation and suppressing TNFα-induced transcriptional activity. This leads to decreased inflammatory cytokine filtration in UUO mice.[19]

MG53 may suppress kidney fibrosis by inhibiting angiogenesis (Figure 2). Angiogenesis is the process of new blood vessel formation from existing vessels. As glomerular and peritubular capillaries are essential for the formation of normal kidney structures and for the functions of glomerular and tubular epithelial cells, capillary endothelial damage and subsequent capillary rarefaction can accelerate glomerulosclerosis and tubulointerstitial fibrosis in all types of kidney disease.[36,37] Conversely, abnormal capillary formation in the kidney, as seen in diabetic kidney disease (DKD), may cause morphological changes in glomeruli and the infiltration of inflammatory cells.[38] Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase that is involved in angiogenesis by activating downstream signaling pathways, such as those of Src, Akt, and ERK1/2.[39] Jinling Dong et al. demonstrated that MG53 can inhibit angiogenesis by regulating the FAK/Src/AKT/ERK1/2 signaling pathway.[40] Moreover, MG53 represses high glucose-induced angiogenesis in human retinal endothelial cells by repressing the EGR1/STAT3 axis.[41]

MG53 relieves CKD-induced muscle atrophy by restoring mitochondrial autophagy.[42] Signaling crosstalk between different organ systems plays an important role in maintaining the normal function of the body.[43,44] Many proteins or cytokines are involved in this crosstalk between signaling, such as activin A, a protein characterized as an endogenous antagonist to the hormone inhibin, and MG53.[42,45] These proteins or cytokines secreted from one organ can lead to functional disorders in other organs and even exacerbate organ disease.[46] Studies have reported that skeletal muscle atrophy and muscle dysfunction are causes of CKD.[47,48] Conversely, patients with CKD who can maintain muscle mass and exercise habits may be able to prevent disease progression and kidney function decline.[49,50] Moreover, emerging evidence suggests that multiple cytokines produced or secreted from the kidneys can give rise to muscle function decline through metabolic acidosis,[51] chronic inflammation,[52] and impaired insulin signaling.[48] Therefore, inhibition of muscle atrophy may prevent CKD progression.[53] Studies have shown that the genetic knockout of MG53 in mice results in muscle dystrophy, along with decreased kidney function.[10,17,23] Moreover, rhMG53 was demonstrated to relieve muscle fibrosis and affect histological structures in a mouse model of muscular dystrophy.[10] Recently, Lijie Gu et al. reported that the expression of MG53 was decreased in the skeletal muscle of a CKD rat model. MG53 overexpression promotes mitochondrial autophagy in vitro, indicating that MG53 alleviates muscle atrophy in CKD by removing abnormal mitochondria.[42]

Thus, MG53 is involved in the inhibition of kidney fibrosis through a variety of signaling pathways, and this may provide a novel strategy for the prevention and treatment of CKD.

4 | MG53 AND METABOLIC SYNDROME-INDUCED KIDNEY INJURY

Metabolic syndrome is a group of disorders that include type 2 diabetes mellitus, obesity, and hypertension. Metabolic syndrome is increasing at epidemic rates and has become one of the most serious threats to human health.[54,55] Diabetes, hypertension, and obesity are common causes of kidney injury.[56–58] Metabolic disorder-induced kidney injury is the most common cause of chronic kidney disease.[59] Insulin resistance is a fundamental pathogenic factor present in metabolic syndrome.[11] Insulin resistance is a systemic disorder that affects many organs and insulin-regulated pathways and can thus cause metabolic syndrome.[60] The insulin receptor is expressed on renal tubular cells and podocytes, and insulin signaling has important roles in podocyte viability and tubular function.[60] Since skeletal muscle is responsible for 70–90% of insulin-stimulated glucose disposal in type 2 diabetes,[61] insulin resistance in skeletal muscle plays a central role in the pathogenesis of metabolic syndrome.[62] Therefore, insulin resistance plays an essential role in metabolic syndrome-induced kidney injury.[60]

MG53 may facilitate kidney injury by promoting metabolic disorders. Numerous studies have revealed that the abundance of MG53 is increased in mice with high-fat diet (HFD)-induced obesity, such as the db/db diabetic mouse model, in spontaneously hypertensive rats, and in nonhuman primates with metabolic syndrome.[63,64] Moreover, the upregulation of MG53 was also confirmed in obese humans and humans with diabetes.[11,65] These results indicate that MG53 plays a positive role in the process of metabolic syndrome. Mechanistically, MG53 acts as an E3 ligase, which is an enzyme that links ubiquitin molecules to a lysine of a target protein, and catalyzes insulin receptor and insulin receptor substrate 1 (IRS1) degradation in a ubiquitin-dependent manner.[65] Thus, it constitutes a central mechanism for controlling insulin signal strength in skeletal muscle.[65] However, Jae-Sung Yi et al. found that MG53$^{-/-}$ mice show an elevated IRS-1 level with enhanced insulin signaling, which protects MG53$^{-/-}$ mice from developing insulin resistance when challenged with a high-fat/high-sucrose diet.[66] Moreover, muscle samples derived from human diabetic patients and mice with insulin resistance show normal expression levels of MG53.[66] They concluded that MG53-induced IRS-1 ubiquitination negatively regulates insulin signaling, which indicates that altered MG53 expression does not serve as a causative factor for the development of metabolic disorders.[66] In addition, Clothilde Philouze et al. found that MG53 is not a critical regulator of the insulin signaling pathway.[67]

Collectively, the relationship between MG53 and renal injury caused by metabolic syndrome remains ambiguous. There are some reasons for this. First, at present, there is still a lack of studies that directly explore the function of MG53 in renal damage caused by metabolic syndrome. Second, the studies in the literature exploring the role of MG53 in metabolic syndrome mainly focus on myocardial or skeletal muscle injury rather than kidney injury.

5 | POTENTIAL CLINICAL APPLICATION OF RHMG53 IN KIDNEY DISEASE

Based on the known renoprotective effects of MG53, rhMG53 protein could potentially be used as a therapeutic approach to prevent, attenuate, or treat acute kidney injury and CKD. Cardiothoracic surgery-associated AKI is a common clinical issue.[3] A recent study suggested that in rodent models of cardiothoracic-associated AKI, the intravenous administration of rhMG53 before I/R is effective in the prevention of AKI.[23] Moreover, rhMG53 (2 mg/kg) can be used as a potential chemotherapeutic agent to avoid the nephrotoxicity of cisplatin in animal models via tail vein injection.[20] Furthermore, rhMG53 (2 mg/kg) attenuated CI-AKI when administered to rats before contrast media by tail vein injection.[20] In addition, rhMG53 (2 mg/kg) plays an effective role in alleviating renal fibrosis in a UUO mouse model.[19] Unfortunately, no study has explored the relationship between the concentration of MG53 and the occurrence of AKI, and the clinical application of rhMG53 has not yet been reported.

Collectively, as MG53 exists in the circulation under normal physiological conditions,[22] the administration of rhMG53 should not elicit an immune response and would be a potent and safe biologic reagent for the treatment of multiple acute tissue injuries.

6 | CONCLUSION

MG53 plays an important role in both AKI and CKD. Its critical function as a membrane repair protein has been clearly demonstrated in PTECs. Moreover, it also appears to mediate the renoprotective effects of several acute kidney injuries and chronic kidney diseases. However, the role of MG53 in podocytes has rarely been reported. The potential utility of rhMG53 as a clinically relevant therapeutic protein is promising and warrants further study.

AUTHOR CONTRIBUTIONS

Wen Shen and Ben Ke provided substantial contributions to the conception of the work, revised the article critically for important intellectual content, and provided the final approval of the submitted version. Both agree to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Xiangdong Fang drafted the article and provided a final approval of the version to be published. Xiangdong Fang agrees to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Jianling Song performed the literature

search and collected the related information. All authors read and approved the final manuscript.

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DISCLOSURE

All authors declare that there are no ethical/legal conflicts involved in this article.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

PATIENT CONSENT FOR PUBLICATION

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