ACUTE KIDNEY INJURY

Mitsugumin 53 mediates repair of damaged proximal tubular epithelium

New research has identified mitsugumin 53 (MG53; also known as TRIM72) as a mediator of cell membrane repair in the proximal tubular epithelium (PTE). This study by Jianjie Ma and colleagues is the first to describe a role for MG53 in renoprotection. The researchers suggest that MG53-mediated repair of PTE cells could be targeted to prevent and treat acute kidney injury (AKI).

Ma and colleagues previously showed that MG53 is an essential component of the cell membrane repair machinery in striated muscle, but the expression and function of MG53 in renal tissue was not examined. In the present study they used an *Mg53*$^{-/-}$ mouse model, and a series of biochemical techniques, to examine the function of *Mg53* in renal protection.

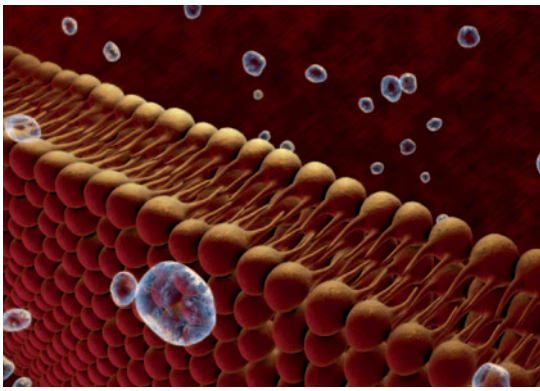
In the first part of their analysis, the researchers found that MG53 is expressed in PTE cells, but not glomeruli, of wild-type mice. Phenotypic characterization of *Mg53*$^{-/-}$ mice identified abnormalities in renal function, including proteinuria at 20 weeks, high urine protein-to-creatinine ratios, and elevated serum creatinine levels, compared to littermate controls. The inner renal cortex displayed numerous pathologies, including pronounced vacuolization, disorganized cisternae, and ~2.5-fold enlargement of the intertubular space. At the ultrastructural level, PTE-specific disorganization of the microvilli and brush border on the apical surface was observed. Finally, *Mg53*$^{-/-}$ mice and derived cultured PTE cells were more susceptible to ischaemia/reperfusion (I/R) and microelectrode penetration injury, respectively, than were wild-type controls. This effect could be rescued *in vitro* upon transfection of *Mg53*$^{-/-}$ PTE cells with functional MG53.

A green fluorescent protein (GFP)–MG53 expression construct was used to evaluate the subcellular localization of MG53 within PTE cells. Under normal conditions, GFP–MG53 localized to the cytosol, intracellular vesicles and plasma membrane. In response to cellular injury, GFP–MG53 translocated to sites of injury on the PTE cell membrane. This effect was recapitulated in human immortalized proximal tubular (HKC-8) cells. Interestingly, a mutated form of MG53 that cannot oligomerize in response to environmental redox changes failed to translocate to injury sites, suggesting that MG53-mediated PTE membrane repair occurs in a redox-dependent manner.

In the second part of their analysis, the researchers investigated whether recombinant human MG53 (rhMG53) could protect against renal injury. Cultured PTE cells were exposed to anoxia/reoxygenation to elicit membrane damage. Exogenous application of rhMG53 to these cells resulted in localization of MG53 to the plasma membrane—an effect that did not occur in uninjured or bovine serum albumin-treated cells.

This process was then modelled at the animal level. In healthy rats, rhMG53 could be detected in the urine 1.5–6 h after intravenous administeration via the tail vein, showing that normal glomeruli are permeable to the protein. Following I/R, albuminuria and serum creatinine levels were reduced in rhMG53-treated rats compared to those administered vehicle. Furthermore, expression of kidney injury molecule-1 (a marker of kidney injury) on PTE cells was notably reduced 5 days after I/R injury in the treated rats, as compared to vehicle controls. These data confirmed that exogenous rhMG53 could ameliorate I/R-induced AKI in rats.

In the final part of the study, the researchers examined whether rhMG53 could prevent the nephrotoxic effects of cisplatin *in vitro* and *in vivo*. They observed that rhMG53 anchored to the PTE cell membrane at the sites of injury caused by cisplatin. This process was mediated by injury-induced exposure of phosphatidylserine on the plasma membrane. Strikingly, mice pre-treated with rhMG53 10 min before cisplatin exposure showed reduced physiologic indicators of renal injury compared to those that were not pre-treated, indicating a renoprotective effect of the recombinant protein.



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At the translational level, the efficacy of cisplatin on promoting cell death and inhibiting tumour growth in mice was not compromised as a result of rhMG53 treatment, and repetitive exposure to rhMG53 did not elicit adverse effects in dogs. The authors propose, therefore, that rhMG53 might be a safe and suitable adjuvant treatment to cisplatin chemotherapy.

"We are communicating with the FDA to bring rhMG53 into human trials for the treatment of AKI," says Ma. "We need to produce high grade rhMG53 for use in trials, and conduct toxicology studies to define its pharmacokinetics, pharmacodynamics, and safety profile. Future studies are planned using large animal models of AKI to establish the efficacy and dosing-range for rhMG53-mediated renoprotection."

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