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NEPHROTIC SYNDROME

ER calcium stabilizers in NS

A growing body of literature indicates that calcium dysregulation is a feature of podocytopathies such as nephrotic syndrome (NS); however, little is known about the role of endoplasmic reticulum (ER) calcium efflux on podocyte health. Using a mouse model of ER stress-induced NS, researchers now show that phosphorylation of the type 2 ryanodine receptor (RYR2) in podocytes leads to calcium leak from the ER into the cytosol, and that ER calcium stabilizers can rescue injurious podocyte responses. "We demonstrate that the ER calcium release channel RYR2 undergoes phosphorylation at Ser2808 during ER stress," explains Ying Maggie Chen. "Most importantly, we identify a chemical compound and a novel biotherapeutic protein that can fix leaky RYR2 and inhibit podocyte injury."

To assess the consequences of ER stress on calcium homeostasis in podocytes, Chen and colleagues used a mouse model of NS caused by podocyte-specific expression of a Cys321Arg mutation in *LAMB2*, which encodes the glomerular basement membrane component laminin β2. Primary podocytes from the mutant mice showed upregulation of proteins associated with ER stress and calcium-mediated apoptosis. Further analyses showed that mutant podocytes had increased RYR2 phosphorylation and ER calcium release. "The accelerated podocyte ER calcium efflux due to leaky RYR2 activates cytosolic protease calpain 2, leading to apoptosis, cytoskeleton disruption and podocyte injury," says Chen.

Assessment of the ER calcium release inhibitor, K201, showed that it inhibited RYR2 hyperphosporylation, attenuated the ER calcium leak and reduced apoptosis in podocytes from mutant mice. In vivo, K201 reduced albuminuria, improved indices of kidney function and prevented the development of podocyte pathology in mutant mice. Similarly, administration of recombinant mesencephalic astrocyte-derived neurotrophic factor (MANF) attenuated apoptosis of mutant podocytes. "Our findings suggest that podocyte ER calcium channel stabilizers are an emerging therapeutic strategy to treat NS caused by ER dysfunction," says Chen. "We plan to move forward with this new class of drugs, and will continue efforts to identify additional ER calcium stabilizers to treat podocytopathies."

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ORIGINAL ARTICLE Park, S. J. et al. Discovery of endoplasmic reticulum calcium stabilizers to rescue ER-stressed podocytes in nephrotic syndrome. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1813580116 (2019)