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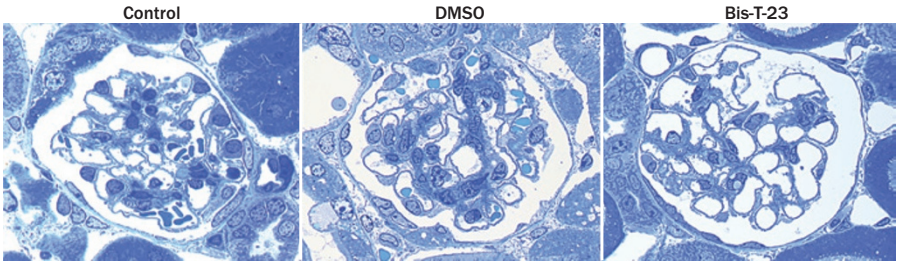
CHRONIC KIDNEY DISEASE

Actin cytoskeleton alterations in podocytes: a therapeutic target for chronic kidney disease

Dysregulation of the actin cytoskeleton following podocyte injury underlies foot-process effacement and progression of renal injury in various forms of chronic kidney disease (CKD). New research demonstrates the therapeutic potential of repairing actin cytoskeleton dynamics by targeting dynamin oligomerization. "The fact that dysregulation of the actin cytoskeleton is a common downstream effect that occurs regardless of the original podocyte injury is well established, and the potential benefit of targeting actin cytoskeleton dynamics has occurred to us as well as to others," explains researcher Sanja Sever. "The finding that it is possible to target the actin cytoskeleton in a specific manner by targeting dynamin in the whole organism is highly unexpected, and strongly suggests that pharmacological targets of dynamin have potential as novel therapeutics in CKD."

The GTPase dynamin is best known for its role in regulating clathrin-mediated endocytosis, but more recently has been recognized for its essential role in regulating podocyte structure and function by binding actin filaments and influencing actin cytoskeleton dynamics. "We discovered an unexpected and highly unusual property of dynamin," says Sever. "Not only could it directly interact with actin filaments but, when oligomerized into higher order structures, dynamin could induce *de novo* actin polymerization, independent of any additional downstream effectors." These findings led her to hypothesize that a small molecule that could specifically promote dynamin oligomerization might have a beneficial effect on injured podocytes via the ability of dynamin to promote actin polymerization.

To examine whether targeting the actin cytoskeleton via dynamin can ameliorate proteinuria and podocyte injury, Sever and Mario Schiffer collaborated to study the effects of genetic manipulation and the small molecule Bis-T-23, which promotes actin-dependent dynamin oligomerization, in zebrafish and diverse rodent models of podocyte injury. In line with previous studies, depletion of the zebrafish dynamin homologue, Dyn2, resulted in gross morphological changes and reduced zebrafish lifespan. Foot-process effacement was also observed, together with a decrease in circulating levels of green fluorescent protein-tagged vitamin D-binding protein (eGFP–DBP), indicative of dysregulated glomerular filtration.



Administration of Bis-T-23 but not DMSO improved glomerular histology in mice with streptozotocin-induced diabetic nephropathy. Permission obtained from Nature Publishing Group © Schiffer, M. *et al. Nat. Med.* doi:10.1038/nm.3843.

Schiffer's group then performed cross-species rescue experiments using wild type and mutated dynamin isoforms to assess whether the zebrafish kidney phenotypes were caused by loss of dynamin. "A cross-species rescue is a powerful tool to test the functional relevance of protein mutations *in vivo*," says Schiffer. Wild type rat and human dynamin, and a mutant human dynamin with increased actin-dependent oligomerization, recovered levels of circulating eGFP–DBP. By contrast, expression of a mutant with decreased actin-dependent oligomerization ($Dyn1^{K/E}$) or an oligomerization-incompetent mutant ($Dyn1^{I690K}$) did not have this effect, demonstrating that actin-dependent dynamin oligomerization is essential for proper glomerular filtration. Administration of Bis-T-23 promoted oligomerization of Dyn2 and restored circulating eGFP–DBP levels in zebrafish expressing $Dyn1^{K/E}$ or $Dyn1^{I690K}$, but only in the presence of endogenous Dyn2, demonstrating that Bis-T-23 directly targets dynamin.

In mice, intraperitoneal administration of Bis-T-23 reduced lipopolysaccharide (LPS)-induced proteinuria. Similarly, administration of Bis-T-23 to cultured mouse podocytes reversed the LPS-induced loss of stress fibers and focal adhesions. To further investigate whether dynamin oligomerization protects against podocyte injury, Sever and colleagues generated mice expressing an inducible dynamin transgene with enhanced propensity to oligomerize. These mice were protected from LPS-induced nephropathy. In addition, Bis-T-23 provided renal protection in various genetic models of CKD and in mice with streptozotocin-induced diabetes. "The fact that dynamin oligomerization directly regulates the actin cytoskeleton and is a druggable target in the whole organism is a concept that most people will find hard to reconcile with their current view of dynamin's role in the cell," notes Sever.

The researchers hope to eventually translate their findings to patients with CKD. "As Bis-T-23 is not suitable for use in humans, we are actively screening libraries to identify a compound with the same biochemical and biological properties that can be used in patients," says Sever.

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