INCONTINENCE

Urothelial β1-integrin knockout suggests mechanosensory mechanism for overactive bladder

It is well understood that disorders of the lower urinary tract are related to miscommunication between the nerves, interstitium, muscle and urothelium, but the exact role of urothelium in the process is not well established. In a recent study published in the *FASEB Journal*, a team led by Warren Hill from Harvard University Medical School, used a selective β1-integrin knockout model to elucidate the role of urothelium as a sensory tissue and determine the mechanism of its communication with sensory nerves.

The team used Cre-LoxP targeted gene deletion to knock out β1-integrin selectively in urothelium. The integrins—transmembrane proteins that physically link the cell to its environment—are involved in the cellular sensing of force, so the team used their knockout model to determine whether the urothelium itself acts as a sensory organ and if urothelial miscommunication leads to symptoms of overactive bladder (OAB).

Sure enough, the knockout mice were incontinent, with abnormal urodynamics on cystometry and a tendency to overfill. Outlet control could not be maintained in the face of rapid detrusor contractions, suggesting that the abnormal communication arises in the urothelium itself. “...One of the most significant aspects to this study is the confirmation that urothelium really is a sensory tissue in its own right, and is able to detect wall tension and then communicate that mechanical information,” Dr Hill told *Nature Reviews Urology*. The exact mechanism by which the urothelium communicates with sensory afferents remains to be clarified, but the authors believe that it might involve ATP. The knockout mice secrete excessive amounts of urothelium-derived ATP into the lumen of the bladder, which if translated to the serosa, could potentially activate purinergic receptors on sensory fibres.

Clinical translation of this study is yet to come, but the authors are hopeful that, if studies in patients with OAB show abnormal integrin signalling, intravesical treatments aimed at targeting integrins in the urothelium could be a new therapeutic option.

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