translational science

PIEZO2, a mechanosensor in the urinary bladder

Philippe Gailly[1] and Olivier Devuyst[1,2]

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The functions of the lower urinary tract to store and eliminate urine are regulated by complex neural pathways that coordinate the activity of the smooth and striated muscles of the bladder, urethra, and urethral sphincters.[1] Besides control by the central nervous system, micturition reflexes are triggered by bladder filling that stretches the bladder wall and by urine flow in the urethra that triggers a urethra-to-bladder reflex facilitating bladder contraction and emptying. Both the urothelium and the mechanically sensitive afferents from the dorsal root ganglia are involved in stretch and pressure detection. The identity of the molecular mechanosensor was previously unknown.

In a study recently published in *Nature*, Marshall *et al.* showed that the ion channel PIEZO2 (FAM38B) acts as a mechanosensor in the bladder urothelium and in innervating sensory neurons.[2] PIEZO2 and its close homologue PIEZO1 (FAM38A) were cloned 10 years ago by Patapoutian and colleagues by using a siRNA-based screen for mechanosensitive ion channels.[3] The PIEZO proteins constitute a class of mechanically gated cation channels, which play critical roles in the sensation of touch, proprioception, and regulation of blood pressure. *In vitro*, PIEZO1 and PIEZO2 both have a high sensitivity to pressure (half activation at ∼30 mm Hg), but they differ in their kinetic characteristics and tissue distribution.[3]

What did the study show?

Marshall *et al.* first showed that PIEZO2 is expressed in >70% of umbrella cells, which constitute the innermost layer of the urothelium, and in >80% of afferent neurons (Figure 1). Umbrella cells form an impermeable barrier and have been shown to respond to membrane stretch by secreting various signaling molecules. Among the latter, adenosine triphosphate (ATP) seems to be the main messenger in the bladder voiding reflex by acting on ionotropic P2X receptors of subepithelial nerve endings.[4] Using different murine models of *Piezo2* conditional knockout, the authors observed that sacral S1 dorsal root ganglion neurons from these mice demonstrated reduced sensitivity to bladder stretch, in particular an absence of sensitivity to pressures <20 mm Hg. Cystometry with urethral electromyography showed that *Piezo2*-knockout mice were less sensitive to bladder filling and displayed irregular micturition timing, longer intervals between bladder voiding contractions, higher pressures just before these contractions, and larger void volumes. These observations suggested that the reflex relaxation of the detrusor muscle in response to progressive bladder filling was impaired or that bladder compliance was attenuated. With age, *Piezo2*-knockout mice developed detrusor hypertrophy, indicative of chronic voiding dysfunction. Coordinated urethral activity was also impaired, indicating that PIEZO2 determines stretch sensitivity in the lower urinary tract and initiates appropriate micturition reflexes.

To discriminate the specific role of umbrella cells and sensory neurons, the authors specifically deleted *Piezo2* in Aδ and C fibers, which are the primary sensory neuron types described in the bladder, or in urothelial cells (Figure 1). Neuron-specific *Piezo2*-knockout mice displayed longer intervals between contractions, but the precontraction pressure was not

[1]*Université catholique de Louvain, Institute of Neuroscience, Cell Physiology, Brussels, Belgium; and* [2]*University of Zurich, Institute of Physiology, Zurich, Switzerland*

Correspondence: *Olivier Devuyst, University of Zurich, Institute of Physiology, Winterthurerstr. 190, CH-8057 Zurich, Switzerland. E-mail: olivier.devuyst@uzh.ch*

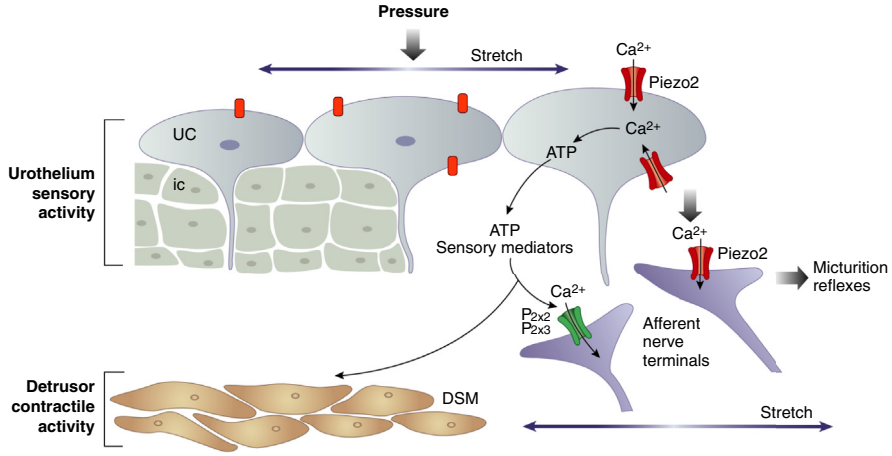

Figure 1 | Localization and physiological function of PIEZO2 in the bladder. PIEZO2 channels (red) are expressed in umbrella cells (UCs) and afferent nerve terminals (Aδ and C fibers). In response to pressure and bladder stretching, umbrella cells release sensory mediators such as ATP that acts on P2X2 and/or P2X3 receptors (green). UCs are involved in reflex relaxation of the detrusor smooth muscle (DSM) during bladder filling. Both UCs and mechanically sensitive afferents from the dorsal root ganglia detect stretch and/or pressure (large arrows) that trigger micturition reflexes. IC, intermediate cell.

different from wild-type mice, emphasizing the predominant role of PIEZO2 in umbrella cells to initiate bladder relaxation. However, neuron-specific *Piezo2*-knockout mice required higher bladder pressure for micturition and demonstrated attenuated urethral contraction, suggesting that neuronal PIEZO2 plays an important role in these reflexes.

Importantly, the PIEZO2 protein also seems to contribute to normal urination in humans. Rare mutations in PIEZO2 cause distal arthrogryposes, a spectrum of disorders including contractures of the distal parts of the limbs.[5] Twelve PIEZO2-deficient patients were reported by the authors: besides deficits in sensory abilities,[6] most of these patients had decreased voiding frequency and sudden urge incontinence.

Why is it important?

The study by Marshall *et al.* establishes PIEZO2 as a mechanosensor in both the bladder urothelium and innervating sensory neurons. PIEZO2 is required for low-threshold bladder-stretch sensing and appears to be involved in both detrusor relaxation during bladder filling and in micturition reflexes. Of note, the lower urinary tract is known to express other mechanosensitive channels such as PIEZO1, which mediates stretch-evoked Ca^{2+} influx and ATP release in urothelial cells,[7] and TRPV4, which is expressed not only in umbrella cells but also in sensory neurons of the sixth lumbar dorsal root ganglia and in detrusor smooth muscle cells.[8,9] All these mechanosensitive channels represent promising therapeutic targets for bladder dysfunction. However, although the role of the bladder urothelium and sensory neurons in mechanosensation is now established, additional studies are needed to understand how pressure sensitivity, distribution, and the signaling pathways triggered by these channels help to coordinate micturition reflexes.

DISCLOSURE

All the authors declared no competing interests.

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