

PERSPECTIVES

Exploring Integrins in Smooth Muscle Function: Addressing Challenging Levels of Complexity and Deciphering Organ-specific Codes of Contraction?

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A perspective on “Deletion of mechanosensory $\beta 1$ -integrin from bladder smooth muscle results in voiding dysfunction and tissue remodeling”

Integrins are transmembrane heterodimers, composed of one of 18 different α and one of eight β subunits.¹ Together with adapter proteins, they accomplish the adhesion of cells with each other and with the extracellular matrix, as well as the attachment of cytoskeletal filaments to membranes.¹ Acting as mechanosensors, they convert mechanical to intracellular signals, for example, tissue deformation and stretch to changes in actin organization.¹ Anchoring of smooth muscle cells within their environment, adhesion of filaments to membranes, and correct actin organization are required for force generation of smooth muscle tissues. Accordingly, promotion of smooth muscle contraction by integrins represents a logical proposition, and since bladder smooth muscle contraction causes bladder emptying, reduced voiding may be expected from integrin deficiency—at least theoretically. As so often in science, the reality is in fact much more complex than presumed, as shown in an article published by Yu and colleagues in a recent issue of *Function*.²

In their current study,² Yu *et al.* examined bladder function and detrusor contractility in mice with a smooth muscle-specific

knockout of $\beta 1$ integrin. In the run-up to the study, they speculated that $\beta 1$ integrin maintains bladder smooth muscle homeostasis by linking actin filaments to the extracellular matrix. In line with their expectation, neurogenic contractions of isolated detrusor tissues were reduced *ex vivo*. In vivo, reduced bladder contractions were confirmed cystometrically. Detachment of actin filaments from membranes, by loss of integrin-mediated connections may provide the simplest explanation, but was obviously not the only mechanism. The knockout of $\beta 1$ integrin caused downregulation of M3 receptors, which mediate neurogenic detrusor contractions and thus, bladder emptying during voiding. In addition, the bladder walls of knockout animals were characterized by profound structural changes, including increased collagen deposition, reduced smooth muscle content, and altered muscle bundle architecture.

It may be even more interesting that the urodynamic phenotype of these $\beta 1$ integrin knockout mice showed impaired bladder emptying, reflected by reduced urine volume per void and paralleled by increased micturition frequency, seen in voiding spot assays and during continuous bladder filling in cystometry. Clinically, increased micturition frequency is a typical sign of detrusor overactivity and overactive bladder (OAB), and summarized with urgency, nocturia, and incontinence as storage symptoms.³ In contrast, impaired bladder emptying is attributed to an underactive bladder and acontractile detrusor,⁴ or to ure-

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Table 1. Reported Roles of Integrins in Regulation of Smooth Muscle Contractility

Tissue	Integrin	Role in Smooth Muscle Contraction	Reference
Detrusor	αV	Procontractile	Luo et al., J Urol 2013;190(4):1421–9
	$\alpha 4$	None	
	$\alpha v\beta 6/Mfge8$	Anticontractile	Kudo et al., Proc Natl Acad Sci U S A 2013;110(2):660–5
Airway	$\alpha 2\beta 1$	Procontractile	Liu et al., J Clin Invest 2021;131(12):e138140
	$\alpha 5\beta 1$	Procontractile	Sundaram et al., J Clin Invest 2017;127(1):365–374
	$\alpha 8\beta 1$	Anticontractile	Khalifeh-Soltani et al., FASEB J. 2018:fj201800109R.
	$\alpha 9\beta 1$	Anticontractile	Chen et al., J Clin Invest 2012;122(8):2916–27
Vascular smooth muscle	$\alpha 5$	Procontractile	Balasubramanian et al., Am J Physiol Regul Integr Comp Physiol 2007;293(4):R1586–94.
	$\alpha 4\beta 1$	Anticontractile	
	$\alpha 9\beta 1$	Anticontractile	Morris et al., Br J Pharmacol 2022; in press
	$\alpha 1\beta 1$	Procontractile	
	$\alpha 4\beta 1$	None	Li et al., Prostate 2020;80(11):831–849
Prostate	$\alpha 9\beta 1$	None	

thral obstruction and benign prostatic hyperplasia (BPH),⁵ which is not the case here. Both conditions are separately addressed by guidelines for diagnosis and management.^{3,4} Multiple forms of incontinence are defined, including mixed types such as urodynamic stress urinary incontinence with urgency, but without detrusor overactivity.³ Conditions including increased micturition frequency and OAB, despite detrusor underactivity or an even acontractile detrusor, are clinically well-known,^{3,4} but still poorly understood and an experimentally underexplored phenomenon. Apparently, relationships between detrusor overactivity, OAB, and storage symptoms are less obvious than commonly believed.^{3,4} Yu et al. now present a phenotype showing ineffective bladder emptying, with simultaneously increased micturition frequency despite detrusor hypocontractility, which is imparted by loss of $\beta 1$ integrin function in the bladder smooth muscle.

Interestingly, another phenotype, again with partly opposing function–symptom relationships, resulting from knock-out of urothelial $\beta 1$ integrin was presented previously by the same group, and was characterized by overflow incontinence and prolonged contraction intervals, but intact detrusor contractility and detrusor hyperactivity.⁶ As now correctly explained by the authors, the relationships between different symptoms, let alone the molecular mechanisms connecting them, are still uncertain, and the intermeshing complexity of different lower urinary tract symptoms is hardly understood. Obviously, however, integrins in the detrusor and urothelium are essential for correct voiding and maintenance of continence.

The impact of the smooth muscle-specific $\beta 1$ integrin knock-out was not limited to the bladder and urodynamic regulation. It also included increased urine production, further contributing to the observed micturition frequency. The reasons for the increased urine production could be alterations in volume homeostasis, in vascular and gut permeability or ureter functions—which are all dependent on smooth muscles. Obviously, regulation of correct smooth muscle function by $\beta 1$ integrin is not limited to the bladder but affects other smooth muscle-rich tissues and organs as well. Thus, if an organ-specific regulation of smooth muscle contraction by integrins exists, it is not attributed to β subunits, but rather imparted by α subunits, of which 18 different subunits exist, resulting in a high number of possible heterodimers.

Regulation of smooth muscle contractility, also including anticontractile functions and at different levels, has been reported from most smooth muscle-rich tissues—but to a limited extent (Table 1).^{7–9} Considering that smooth muscle contraction is essentially involved in diseases with high prevalence, high mortality, and enormous socioeconomic costs, representing a major target for their medical treatment, it is surprising that integrin functions have been so rarely examined. The world wide number of patients with smooth muscle-based diseases amounts to 1–3.4 billion patients with arterial hypertension, 1 billion patients with lower urinary tract symptoms (LUTS), and >500 million patients with obstructive lung diseases, with numbers from impaired kidney function in diabetes, portal hypertension in liver cirrhosis, erectile dysfunction, or pulmonary hypertension not yet included. Drug development is often focused on receptor antagonists or agonists. Application of available LUTS medications may be limited by side-effects and poor efficacy. Treatment of storage symptoms in OAB with muscarinic antagonists is afflicted with discontinuation rates around 90% and low efficacy. Considering that increased micturition frequency was observed despite downregulation of M3 receptors in $\beta 1$ integrin knockouts, it may not be surprising that numbers of nonresponders during treatment with antimuscarinics amount to 50% or less for increased frequency and incontinence, and around 80% for urgency.¹⁰ For treatment of voiding symptoms in BPH, major attempts were made to optimize the subtype-selectivity of $\alpha 1$ -blockers, as side-effects arise mostly from effects on cardiovascular $\alpha 1$ -adrenoceptors. In addition, their efficacy is limited by nonadrenergic mediators of contraction, keeping prostate smooth muscle tone in BPH elevated despite treatment with $\alpha 1$ -blockers; however, their inhibition would cause even more and deleterious side effects, due to their systemic relevance.

Identifying organ-specific targets for potential drug treatment of smooth muscle-based diseases would be a substantial advance, at least in the context of LUTS. Could the key be an organ-specific code of smooth muscle contraction, imparted by organ-specific composition of integrin dimers, which just needs to be deciphered for the development of organ-specific drugs? Probably, this is an illusion rather than a realistic vision, but it can only be answered by more studies. The current study of Yu et al. is exciting and indicates

that further such investigations may uncover different levels of complexity.

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Conflict of Interest

The author has no conflict of interest.

References

1. Bachmann M, Kukkurainen S, Hytonen VP, Wehrle-Haller B. Cell adhesion by integrins. *Physiol Rev.* 2019;**99**(4):1655–1699.
2. Weiqun Y, Bryce M, Lanlan Z., et al. Deletion of mechanosensory β 1-integrin from bladder smooth muscle results in voiding dysfunction and tissue remodeling. *Function.* 2022;**3**(5):zqac042.
3. Nambiar AK, Arlandis S, Bã K, et al. European association of urology guidelines on the diagnosis and management of female non-neurogenic lower urinary tract symptoms. Part 1: diagnostics, overactive bladder, stress urinary incontinence, and mixed urinary incontinence. *Eur Urol.* 2022;**82**(1):49–59.
4. Arlandis S, Bã K, Cobussen-Boekhorst H, et al. European association of urology guidelines on the management of female non-neurogenic lower urinary tract symptoms. Part 2: underactive bladder, bladder outlet obstruction, and nocturia. *Eur Urol.* 2022;**82**(1):60–70.
5. Oelke M, Bachmann A, Descazeaud AL, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol.* 2013;**64**(1):118–140.
6. Kanasaki K, Yu W, Bodungen M, et al. Loss of beta1-integrin from urothelium results in overactive bladder and incontinence in mice: a mechanosensory rather than structural phenotype. *FASEB J.* 2013;**27**(5):1950–1961.
7. Joseph C, Tatler A. Pathobiology of airway remodeling in asthma: the emerging role of integrins. *J Asthma Allergy.* 2022;**15**:595–610.
8. Li B, Wang X, Wang R, et al. Inhibition of neurogenic and thromboxane A2 -induced human prostate smooth muscle contraction by the integrin alpha2beta1 inhibitor BTT-3033 and the integrin-linked kinase inhibitor Cpd22. *Prostate.* 2020;**80**(11):831–849.
9. Morris GE, Denniff MJ, Karamanavi E, et al. The integrin ligand SVEP1 regulates GPCR-mediated vasoconstriction via integrins alpha9beta1 and alpha4beta1. *Br J Pharmacol.* 2022. **179**(21):4958–4973. doi:10.1111/bph.15921.
10. Muderrisoglu AE, Oelke M, Schneider T, Murgas S, De La Rosette JJMCH, Michel MC. What are realistic expectations to become free of overactive bladder symptoms? Experience from non-interventional studies with propiverine. *Adv Ther.* 2022;**39**(6):2489–2501.