The bladder mucosa consists of the urothelium, basement membrane, and lamina propria (LP). Although the urothelium has been given much attention, it may be regarded as one part of a signaling system involving another equally important component of the bladder mucosa, namely, the LP. The LP lies between the basement membrane of the mucosa and the detrusor muscle and is composed of an extracellular matrix containing several types of cells, including fibroblasts, adipocytes, interstitial cells, and afferent and efferent nerve endings. In addition, the LP contains a rich vascular network, lymphatic vessels, elastic fibers, and smooth muscle fascicles (muscularis mucosae). The roles of the LP and its components in bladder function have not been definitively established, though it has been suggested to be the capacitance layer of the bladder, determining bladder compliance and enabling adaptive changes to increasing volumes. However, the bladder LP may also serve as a communication center, with an important integrative role in signal transduction to the central nervous system (nociception, mechanosensation). The LP may also, by means of its different components, make it possible for the urothelium to transmit information to other components of the bladder wall, contributing to activation of the detrusor muscle. In addition, the LP may serve as a source for production of factors influencing the growth of both the overlying urothelium and the underlying detrusor muscle.

The bladder ECM is a structure continuously undergoing remodeling, to which cells attach and respond, leading to adhesion, production of matrix components, growth, migration, or differentiation. The matrix is a structural scaffold of proteins, proteoglycans, and glycosaminoglycans that provides support and signaling to the cells of the bladder. The different ECM components include collagen I and III, which represent the bulk of the proteins. In normal bladders, the collagen composition is approximately 25% type III collagen and 75% type I collagen (type III:I ratio is 1:3). Fibrillar collagens are localized mainly to the LP and endomysia that surround bladder smooth muscle cells and provide structure, tensile strength, and—through complex coiling—compliance. In the unfilled bladder, type III collagen fiber distribution is largely isotropic, and the architecture is that of a loose network of fibers grouped into small strands, with relatively few thick bundles. In the LP (and detrusor), the ECM is largely a meshwork of loose, wavy fibers without uniform orientation. As the bladder fills, the type III collagen fibers in the LP undergo a change in orientation, becoming parallel to the urothelium, while those in the

Key words: afferent nerves; arterioles; interstitial cells; receptors; venules
detrusor become oriented orthogonally to the urothelium and muscle bundles. It has been suggested that collagen in the bladder LP exerts a critical mechanical function. Elastic fibers in the bladder allow the bladder to recoil to its original shape after micturition. Deficiencies in elastogenesis can affect bladder function. Adhesive proteins—including laminins and fibronectin, glycans and glycoproteins, and various ECM receptors—have been demonstrated; their roles are discussed extensively elsewhere. Bladder LP has been used as biomaterial for various reconstructive procedures, due to its biocompatibility and regenerative potential. Collagen-based tissue matrices are known to possess essential characteristics required for tissue regeneration, including bioactive substances that are contained within the matrix, such as growth factors, adhesion molecules, and modulators of coagulation and fibrinolysis. These factors are believed to enhance cell viability and tissue regeneration.

Chun et al. identified at least 10 growth factors preserved in the decellularized pig bladder LP, including VEGF, BMP4, platelet-derived growth factor receptor (PDGF)-BB, KGF, TGFβ1, IGF, bFGF, EGF, and TGFα. The soluble LP extracts produced a conspicuous effect on cell proliferation when added as a supplement in vitro. These findings demonstrate that growth factors and ECM in the bladder LP maintain valuable biological activity even after decellularization and extraction processes. After observing that bladder LP cells exhibited a high level of proliferation, Soler et al. designed a study to evaluate the effect of these cells on the proliferation of urothelial and smooth muscle cells. The authors isolated urothelial, smooth muscle, and LP cells from porcine bladders using established harvesting techniques. Cell populations from each source were culture expanded in their growth media. The cultured cell populations were characterized using cell-specific antibodies. Urothelial and/or smooth muscle cells were grown under three different conditions: (1) cultured on a feeder layer of mitomycin C-treated LP cells to assess juxtacrine effects, (2) cultured in the presence of LP cells grown on a porous membrane to assess paracrine effects, and (3) grown on regular tissue culture plates (control). LP cells accelerated the growth of both urothelial and smooth muscle cells through cell-cell (juxtacrine) or factor-mediated (paracrine) interactions (Figs. 2 and 3).

**INTERSTITIAL CELLS AND LOCAL SIGNALING**

The LP contains novel cell populations, described in the literature as IC, interstitial cells of Cajal (ICC), or myofibroblasts and referred to here simply as IC. IC within the LP form networks interconnected by Cx43 gap junctions and are associated with mucosal nerves. A layer of IC is found at the base of the urothelium, and these cells are usually referred to as suburothelial IC (Ross A. Davidson and Karen D. McCloskey, unpublished observations; Fig. 4). IC-LP have been identified with antibodies to KIT, vimentin, and more recently, PDGFRα (Dr. Louise Johnston and Dr. Karen D. McCloskey, unpublished observations; Fig. 5), and confocal microscopy. In guinea-pig bladder, there is some overlap between KIT+ and PDGFRα+ IC-LPs, whereas there is apparently no overlap in murine bladder, similar to gastrointestinal tissues, where there are reportedly two separate populations of KIT+/PDGFRα−/ICC and KIT+/PDGFRα+ fibroblast-like cells. In the bladder, the KIT+ and/or PDGFRα+ IC-LP seem to constitute a subpopulation of the total vimentin-expressing IC-LP. The physiologic significance of the expression of combinations of the marker proteins within IC-LP is not yet known but may be linked with specialization of roles.

The ultrastructural profile of the bladder IC is comparable with that of the gastrointestinal IC, but in normal tissues, the bladder IC has only a partial overlap with myofibroblasts;...
specifically, myosin and desmin filaments and the fibronexus are absent, leading some to suggest that the myofibroblast phenotype is not present in the normal bladder. Myofibroblasts are considered to be smooth muscle-like fibroblasts found in many tissues of the body, where they have functions in growth, repair, and wound healing. It is not yet known whether IC-LP change to a myofibroblast phenotype under pathophysiologic stresses, such as inflammation or ischemia, but it has recently been reported that suburothelial IC change to a fibroblastic phenotype in bladder pain syndrome and in the neurogenic bladder.

For more than a decade, the literature has debated whether IC could pace bladder smooth muscle spontaneous activity. The available data do not easily support a pacemaking role for detrusor-layer IC, and it is possible that detrusor IC may act as a "brake," preventing coordinated smooth muscle contraction during filling. While detrusor smooth muscle itself exhibits spontaneous contractile, electrical, and calcium signaling activity, there is reason to believe that this activity is modulated by cells within the LP. The available evidence suggests that IC-LP possess physiologic properties, consistent with a role in normal bladder physiology. Functional expression of calcium-activated chloride channels underpinning spontaneous transient depolarizations is consistent with a pacemaking role, as has been shown for

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**Fig. 3.** Juxtacrine effect of LP cells on cultured pig urothelial and smooth muscle cells. Data from Soler et al. LP, lamina propria.

**Fig. 4.** A: Epifluorescent micrograph of the guinea-pig urothelium. Nuclei stained with DAPI, cells labeled with phalloidin. B: Confocal reconstruction through the guinea-pig urothelium (red) showing KIT+ suburothelial interstitial cells (green) at the base of the urothelium. Figure courtesy of Dr. Ross A. Davidson and Dr. Karen D. McCloskey, unpublished observations. PDN, phalloidin.
gastrointestinal and urethral IC. Ex vivo myographic recordings from bladder strips, which have had the mucosal layer (i.e., LP and urothelium) removed by sharp dissection, demonstrate non-neurogenic, myogenic spontaneous contractions maintained for several hours. Similar experiments on intact full-thickness bladder wall strips show more robust activity, that is, greater amplitude, indicating that the presence of LP cells exerts a positive modulatory influence on the detrusor smooth muscle (Dr. Kevin P. Monaghan and Dr. Karen D. McCloskey, unpublished observations; Fig. 6). The underlying mechanisms of the physiologic relationship between the LP and the detrusor smooth muscle are not yet known.

The hypothesis that IC-LP are involved in the modulation of detrusor smooth muscle activity appears to be strengthened by data on the pathophysiologic bladder. Mucosa-intact tissue strips from neurogenic, overactive diabetic rat bladder were found to have better developed spontaneous contractions than controls (Dr. Kevin P. Monaghan and Dr. Karen D. McCloskey, unpublished observations; Fig. 6). Removal of the mucosal layer from control and diabetic strips resulted in lower amplitude spontaneous contractions indicating that cells from the mucosal layer were amplifying, or acting to increase the amplitude of smooth muscle contraction. Furthermore, an association between bladder overactivity and increased IC-LP has been reported for obstructed guinea-pig bladder and human neurogenic and idiopathic overactive bladder.

Interestingly, purinergic stimulation of IC-LP activates calcium-activated chloride currents, suggesting that local purines, released from the urothelium or mucosal nerves, could drive the IC-LP potential pacemaking activity. Morphologic studies showing that IC-LP are found close to nerve endings containing both clear and dense-cored vesicles or clear vesicles alone suggest that IC-LPs could physiologically interact with both efferent and afferent nerves. A recent study of guinea-pig mucosal whole-mount preparations, loaded with a calcium indicator and imaged with fluorescence microscopy, provided evidence that IC-LP are functionally innervated. Electrical field stimulation evoked simultaneous Ca\(^{2+}\) transients in multiple neighboring IC-LP which had been firing nonsynchronous Ca\(^{2+}\) oscillations prior to neurogenic stimulation, suggesting the nervous system may override the background signaling of the IC-LP.

Several observations indicate that IC-LPs could be involved in the coordination of local bladder signaling processes. Mukerji et al. reported muscarinic (M\(_2\) and M\(_3\)) receptor immunoreactivity on cells in the LP resembling IC, a finding confirmed by Grol et al. Mukerji et al. suggested these cells could respond...
to cholinergic signaling. However, Sui et al.36 reported that suburothelial IC did not respond to carbachol, but application of adenosine triphosphate (ATP) elicited Ca\(^{2+}\) transients. P2Y\(_{6}\) receptors may mediate these excitatory responses.26,36 Further studies on spinal cord injured (SCI) rats, where IC-LPs are upregulated, suggested that this effect of ATP and other P2Y agonists could increase spontaneous contractile activity in the bladder.37 Xue et al.38 demonstrated that vimentin\(^{+}\) (and some KIT\(^{+}\)) IC-LPs in the human bladder expressed hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, particularly HCN4. This channel is specialized for the I\(_{h}\) current, which is a characteristic of pacemaker cells, and it was suggested that HCN4 could be involved in the generation of spontaneous bladder activity during filling. However, further functional studies are needed to put these data into proper perspective.

Studies have concluded that IC-LPs may be associated with many other signaling systems. Nile et al.39 found stretch-independent regulation of prostaglandin (PG) E\(_{2}\) production within the isolated guinea-pig LP, and Rahnama et al.40 demonstrated IC expression of PG\(_{E_{2}}\) receptors (EP1 and EP2), indicating that the cells can respond to PG\(_{E_{2}}\). Both cyclooxygenase (COX)-1 and COX-2 have been found in urothelial cells, making them a possible site of PG synthesis.41 In a murine model, elevated COX-2 expression in the urinary bladder produced upregulated inflammatory response and induction of cell proliferation.42 Thus, both COX enzymes and PGs produced by the urothelium and/or LP, may represent therapeutic targets. Nile and Gillespie43 demonstrated complex signal interactions within the guinea-pig urothelium/LP, involving acetylcholine (ACh), ATP, nitric oxide, and PG\(_{E_{2}}\). When exposed to stretch, PG\(_{E_{2}}\), or an ATP analog, the bladder preparations released ACh. Concentration-dependent production of PG\(_{E_{2}}\) was induced by the muscarinic receptor agonist arecaidine and was inhibited in a dose-dependent manner by an M\(_{3}\) receptor antagonist (AFDX-116)—but not by an M\(_{3}\) receptor antagonist (darifenacin) nor the nitric oxide donor NONOate.

Johnston et al.44 found that the microvessels in the LP were associated with KIT\(^{+}\) IC and suggested the existence of an IC–vascular coupling. Hashitani et al.45 reported that although suburothelial arterioles were quiescent, there were spontaneous action potentials and vasoconstrictive activity in suburothelial venules. The authors speculated that adjacent perivascular IC could have a role in generating spontaneous venular vasoconstriction. It seems reasonable to consider that perivascular IC could be physiologically involved in local control of bladder tissue perfusion.

The function(s) of bladder IC are incompletely understood, and it seems that IC-LP and detrusor IC may serve different functions. Because of their localization, IC-LP have been suggested to form structural and physiological links between urothelial cells, sensory nerves, and/or and detrusor smooth muscle cells.45,46 Moreover, IC-LP might be involved in the pathophysiology of bladder disorders, for example, the neurogenic bladder, and in interstitial cystitis, where local signaling processes are considered to be important.22,47

**NERVES WITHIN THE LP**

The bladder LP contains both afferent and efferent nerves. Gabella and Davis55 described the general distribution of afferent nerves using whole-mount preparations of the rat bladder with calcitonin gene-related peptide (CGRP) immunoreactivity as a marker. CGRP-immunoreactive (IR) axons formed an elaborate suburothelial plexus, located very close to the LP capillary network, but the two patterns appeared to be unrelated. The distribution of CGRP-IR nerves varied markedly in the different regions of the bladder. Thus, in the cranial regions, the suburothelial plexus was absent, and the mucosa contained only a few perivascular CGRP-IR axons. In the equatorial regions, the CGRP-IR axons were less abundant than in the caudal region. The bladder neck and the initial part of the urethra exhibited the highest density of mucosal innervation. Here, the axons of the suburothelial plexus were very close to the urothelium, and the finest, which were also the most distinctly varicose, ran parallel to and in apparent contact with the urothelium. These axons issued thin side-branches that penetrated the urothelium (intraurothelial axons); some penetrated almost the full thickness of the urothelium.

El-Badawi and Schenk46 described ACh-esterase\(^{+}\) nerves in the bladder LP, and further studies by Gosling and Dixon50 found a marked regional variation in distribution. Similar to the distribution of CGRP-IR terminals, few ACh-esterase\(^{+}\) nerves were found in the LP of the fundus and adjacent parts of the bladder body. However, in the lower part of the body and bladder neck, their numbers gradually increased. An extensive plexus adjacent to the urothelial lining was observed throughout the bladder neck itself.50 Nerve cell bodies were not found in any part of the LP in any of the species investigated (guinea-pigs, rats, rabbits, and cats). However, ganglion cells positive for choline acetyltransferase and CGRP were demonstrated in the guinea-pig LP.51 In the human bladder, intramural ganglion cells were found in the LP or embedded among the detrusor muscle bundles.52 The majority of the ganglia were small in size and contained from one to six neurons, and the ganglion cells possessed the fine structural characteristics of parasympathetic nerve cells.53

The function of the ACh-esterase\(^{+}\) nerves in the LP is not known, but it has been proposed that they are involved in sensory mechanisms.50 Investigations by Smet et al.54 revealed the complexity of LP innervation in the human bladder. They studied the distribution of nerves containing CGRP, substance P (SP), neurokinin A (NKA), and vasoactive intestinal peptide (VIP) using single- and double-label immunohistochemistry and found that nerves containing CGRP and tachykinins were typically present within the suburothelial region, surrounding the intramural ganglia, and around the blood vessels. These nerves were sparsely distributed and only very rarely projected to the smooth muscle bundles of the detrusor. In contrast, VIP-containing nerves formed a dense suburothelial plexus and also projected to the detrusor muscle bundles. At least three neurochemically distinct populations of nerves could be discriminated containing predominantly either VIP\(^{−}\)–, CGRP\(^{−}\), or CGRP/SP/\(^{±}\) NKA. In the human bladder, Gosling and Dixon50 demonstrated noradrenergic nerves in the LP, which are considered to have a vasomotor function. Similar tyrosine hydroxylase\(^{+}\) nerves have been identified in the dog bladder.55

Both afferent and efferent nerves in the LP show changes in pathologic conditions. For example, Apodaca et al.56 studied the effects of spinal cord injury on several indicators of urothelial barrier function. They found significant disruption of the urothelial permeability and accompanying changes in morphology within 2 hr after production of injury, but they also demonstrated that these early changes could be prevented by pretreatment with hexamethonium, indicating involvement of sympathetic and/or parasympathetic efferent input to the bladder. Prior treatment with capsaicin worsened the effect of SCI on urothelial permeability, and the authors suggested that capsaicin-sensitive afferents may play a protective role in the process.

Smet et al.54 found that in the bladders of women with urodynamically proven idiopathic detrusor overactivity, the
density of CGRP and SP-IR nerves within the LP was increased by 82% and 94%, respectively, relative to that of bladders from women with no symptoms of frequency or urgency. This effect was not due to an increase in overall nerve density; immunoreactivity for the general nerve marker PGP 9.5 was not significantly different between the two groups. The authors suggested that the results indicated that at least some patients with detrusor overactivity demonstrated increases in a specific class of nerve fibers containing CGRP and SP. It is possible that the nerves within the LP serve both afferent and efferent functions and, in addition, may be involved in a complex signaling network forming local reflexes that also include the urothelium, IC, vessels, and other structures within the bladder wall.51

MUSCULARIS MUCOSAE

Early textbooks of histology categorically stated that a muscularis mucosa is absent from the human urinary bladder. The existence of this structure in the human bladder was first described by Dixon and Gosling,5 and Ro et al.57 confirmed and further clarified this observation. The constituent smooth muscle bundles are irregularly arranged and form a discontinuous layer, which might explain why the presence of a muscularis mucosa was not widely recognized. The muscularis mucosae consists of irregularly arranged muscle bundles composed of relatively small-diameter smooth muscle cells. These cells are both morphologically and histochemically distinct from those forming the detrusor muscle, being rich in nonspecific cholinesterase and glycogen. However, like the detrusor muscle, the muscularis mucosa is richly supplied with ACh-esterase+ nerve fibers.

Concerning the possible functional significance of a muscularis mucosa in the human urinary bladder, one can only speculate. The electron microscopic observation of large numbers of elastic microfibrils in close association with the smooth muscle cells of the muscularis mucosa could be interpreted as indicating that such cells are actively involved in the synthesis and secretion of connective tissue components. Like muscularis mucosae of the gut, the bladder muscularis mucosae could possibly be involved in causing localized movements of the mucosal lining, although this seems rather unlikely in view of its discontinuous nature.

Furthermore, it is difficult to appreciate the need for such a mechanism in the bladder. Dixon and Gosling5 suggested that the presence of a muscularis mucosa in the bladder wall may have an embryologic explanation, because both the bladder and intestines are hindgut derivatives. However, it is curious that a similar muscularis mucosa has been demonstrated only in the guinea-pig bladder58 and not in the bladders of other mammals, such as rat, rabbit, cat, or dog.5 Heppner et al.58 characterized the properties of the muscularis mucosa in mucosal strips of guinea-pig bladder, describing the muscularis mucosae as composed of a discontinuous band of smooth muscle sheets and bundles, located in close proximity to the urothelium. These muscle cells expressed smooth muscle α-actin. Mucosal strips exhibited spontaneous phasic contractions (SPCs) that were attributed to the smooth muscle of the muscularis mucosae. The SPCs seemed to result from bursts of Ca2+ (flashes). The force of SPCs generated by the mucosal layer was equivalent to that of detrusor SPCs; however, the peak force of detrusor contractions evoked by 60 K+ was ~40-fold greater than that of the muscularis mucosae. In contrast to the detrusor, the mucosal layer exhibited very little activity of the small-conductance Ca2+-activated K- or large-conductance Ca2+-activated K+ channels. Heppner et al.58 suggested that the muscularis mucosae is functionally distinct from the detrusor and may contribute to bladder physiology, for example, by increasing the nonvoiding contractions found in certain bladder pathologies.

Sadananda et al.59 investigated the contractile properties of pig bladder mucosa (urothelium and LP). Their mucosal strips contracted in response to carbachol and NKA even if the urothelium had been destroyed by protamine sulphate and trypsain. They found immunostaining for smooth muscle actin and vimentin in a discreet layer under the urothelium, within small muscle bundles in the mucosa, as well as in mucosal blood vessels. However, the authors identified suburothelial myofibroblasts to be the cell type mediating mucosal contraction. Moro et al.60,61 found that the mucosa (urothelium and LP) from guinea-pig bladders exhibited a spontaneous contractile activity that was increased during stretch. The mechanism appeared to involve endogenous ACh release acting on M3 muscarinic receptors; however, the actions of ACh in the guinea-pig urothelium/LP may involve both M3 and M2 receptors, as it was shown that methoctramine (M3-receptor-selective antagonist) significantly decreased carbachol-induced tension. It is unclear what structures within the preparation were responsible for the contractile activity of the mucosal strips; participation of the muscularis mucosae, the smooth muscle of the LP vessels, and the IC cannot be excluded.

VASCUATURE

Since the barrier function of the urothelium and contractile functions of the detrusor depend on adequate supply of oxygen and nutrients from the blood, the blood vessels in the bladder wall must be capable of adapting to the spatial changes resulting from the filling/voiding cycle without compromising the blood flow. Few studies have been performed on the (micro) anatomy of human bladder vessels. Miodoski and Litwin62 performed a corrosion-casting study on the human bladder wall. They identified two major vascular plexuses (adventitial/serosal and mucosal) and distinguished two distinct capillary networks (muscular and suburothelial) in the successive layers of the wall. The striking feature of the majority of bladder vessels, aside from the capillaries, was their tortuosity, ranging from waviness to tight coiling. The mucosal plexus consisted of some capillaries, thin arteries (50–100 μm), and more numerous, thicker veins (80–250 μm), showing a tortuous appearance and frequent interlacements; it formed a distinct vascular layer parallel to the inner surface of the bladder and following the profiles of mucosal folds (Fig. 7). The authors observed that the mucosal plexus followed the folds parallel to their surface. Further, it gave off short, straight, mostly perpendicular twigs that communicated with the suburothelial capillaries. The suburothelial capillary network manifested capillaries of “extreme density” and “uneven contours,” while in less-folded areas of the trigone and urethral orifice, the network was looser, and the capillaries were thinner. In contrast, the capillary system within the detrusor muscle layer was poorly developed.

Suburothelial microvessels may have a role in maintaining microcirculation to cells involved in bladderafferent signaling. Hashitani et al.44 investigated the properties of these microvessels and found that suburothelial venules, but not suburothelial arterioles, showed spontaneous action potential and vasoconstriction activity. They also found that cyclophosphamide (CPA) or nicardipine prevented venular vasoconstriction, while diphenylborate, niflumic acid, or DIDS decreased it. The authors noted spontaneous Ca2+ transients in venular smooth muscle cells and in perivascular IC, and nicardipine decreased the amplitude and disrupted the synchronicity of these Ca2+ transients.
transients. Residual Ca\(^{2+}\) transients in nicardipine occurred asynchronously and were abolished by CPA. Suburothelial arterioles constricted in response to transmural nerve stimulation, and the response was sensitive to tetrodotoxin 1\(\mu\)M. Prazosin or the selective \(\alpha_{1A}\) blocker RS17053—but not the \(\alpha_{1D}\) blocker BMY7378—suppressed these constrictions, and any remaining constrictions were abolished by guanethidine. These findings give some insights of LP vascular control mechanisms; however, their importance for normal and pathologic bladder function remains to be established.

LYMPH VESSELS

Using antibodies against the lymphatic vessel endothelial hyaluronan receptor (LYVE-1), Matsumoto et al. demonstrated the distribution of lymphatic vessels in the human bladder. Small lymphatics expressing LYVE-1 were distributed in all layers of the normal bladder except for the urothelium. The border areas—the LP and detrusor or the detrusor and adventitia—showed the greatest distribution of these vessels. The small vessels were irregular in shape and without thick walls. The density of the lymphatics in the detrusor was significantly greater than in other parts of the bladder wall.

CONCLUSION

The LP is essential for bladder function, both normally and in various bladder disorders. The LP acts as the capacitance layer of the bladder wall, determining bladder compliance and enabling adaptive changes to increasing volumes, while the detrusor functions as the "limiting" or "girding" layer to prevent overdistension. However, the bladder LP may also have a central integrative role, for example, in signal transduction (nociception, mechanosensation), and it may be a source for production of factors influencing the growth of both the overlying urothelium and the underlying detrusor muscle.

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Fig. 7. Vessels in the lamina propria. Asterisk denotes avascular areas. From Miodoski and Litwin. AP, adventitial plexus; MP, mucosal plexus; P, perpendicular vessel; SCP, suburothelial capillary plexus.
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