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LETTER TO THE EDITOR

Prostate Disease

Re-epithelialization of the prostatic urethra after two-micron laser resection of the prostate

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Dear Editor,

Benign prostatic hyperplasia (BPH) is the most common genitourinary tract disease in elderly males.[1] The two-micron laser combines the advantages of efficient resection and rapid vaporization, resulting in high-performance resection and excellent hemostasis in resection of the prostate adenoma, which makes it an effective and promising modality in BPH treatment.[2] However, severe edema and necrosis of the remaining prostatic tissue after vaporesection of the prostatic adenoma may cause severe irritative and/or obstructive symptoms and may even result in the need for a second operation. Rapid wound re-epithelialization in the prostatic urethra can, however, reduce the incidence of postoperative complications after transurethral resection of the prostate (TURP).[1]

It is generally considered that re-epithelialization of the prostatic urethra after TURP initiates from normal epithelial cells of the bladder neck, which proliferate and differentiate to seal the wounds. Nevertheless, Orihuela *et al*.[3] demonstrated that it was the germinal epithelium in the remaining prostatic glands and ducts that dominated the healing process; however, the exact healing mechanism at the molecular level remains unknown.

Stem cells are defined as undifferentiated cells that can self-renew and differentiate. To date, stem cells have been detected in individuals at all development stages as well as in multiple organs and tissues of adults.[4-6] Azuma *et al*.[7] grafted matrigel containing freshly isolated epithelial and interstitial cells from adult prostate subcutaneously into the flank of nude mice, and prostatic duct-like structures were observed. Kyprianou and Isaacs[8] found a rapid reduction in the total prostate volume due to programmed death of androgen-dependent prostatic epithelial cells, with only basal cells surviving in castrated mice. However, this trend was reversed, and the prostate restored in size and function upon testosterone administration. The study suggested that the basal-cell layer contains stem cells are responsible for the development, maturation and function of the prostate. Thus, we tried to investigate the mechanism of re-epithelialization of the prostatic urethra after transurethral two-micron laser resection of the prostate (TmLRP) in a canine model by focusing on the healing process, epithelial origin of the prostatic urethra, and the role of basal-cell-layer-related stem cells.

Thirty adult cross-breed male dogs (age 5–7 years; weight 18–22 kg) were established a model of TmLRP using the RevoLixTM 2-μm laser device (the wavelength 2.013 μm, and an energy of 70 W) after anesthetized with an intraperitoneal administration of 10% chloral hydrate (0.3 ml per 100 g). The animals were taken biopsies from the bladder neck, prostatic urethra, and urethral mucosa in the verumontanum (prostate apex) under the cystoscopy and postoperation after TmLRP. Also, specimens were examined using hematoxylin-eosin staining and immunohistochemistry.

Under the cystoscopy, no normal mucosa of the prostatic urethra remained, and the wounds had a burnt-like appearance after TmLRP. At day 3, no epithelia covering the wounds. At day 5 to day 10, from small numbers of scattered insular epithelial-cell clusters to thin layers of epithelial cells were observed covering the wounds. There was still no evidence of epithelial migration from the bladder neck or proximal end of the verumontanum. After 2 to 8 weeks, the wounds were completely covered by integral epithelia and had become redder. There were clear boundaries between newly formed epithelia and those of the bladder neck and proximal end of the verumontanum (data not shown).

Compared with normal specimens (**Figure 1a**), isolated epithelial cells were scattered in the surface of the necrotic tissues at day 3 (**Figure 1b**). At day 5, overlying insular epithelial cell clusters were found (**Figure 1c**). At day 7, Punctate and lamellar epithelial cells were observed overlying the surface of the necrotic tissues (**Figure 1d**). At day 10, the wounds were covered with a thin layer of irregularly arranged epithelial cells of variable shape and size (**Figure 1e**). Two to four weeks after surgery, the wounds were covered with an overlying epithelium with a varying number of cell layers from 2 or 3 layers to 6–8 layers (**Figure 1f and 1g**). After 8 weeks, the prostatic urethra was covered by a mature epithelium consisting of cells with polarity (**Figure 1h**).

Compared with normal specimens (**Figure 1i**), UPs were positively stained in the cytoplasm of urothelial cells. Our results showed a few scattered UPs-positive cells distributed in the surfaces of the remaining prostatic tissues 3 days after TmLRP (**Figure 1j**). After 5 and 7 days, the UPs started appearing in the borders of the tubular and follicular cells (**Figure 1k** and **1l**), while at day 10, a layer of UPs emerged in the wound surface (**Figure 1m**). Complete urothelia with a polar

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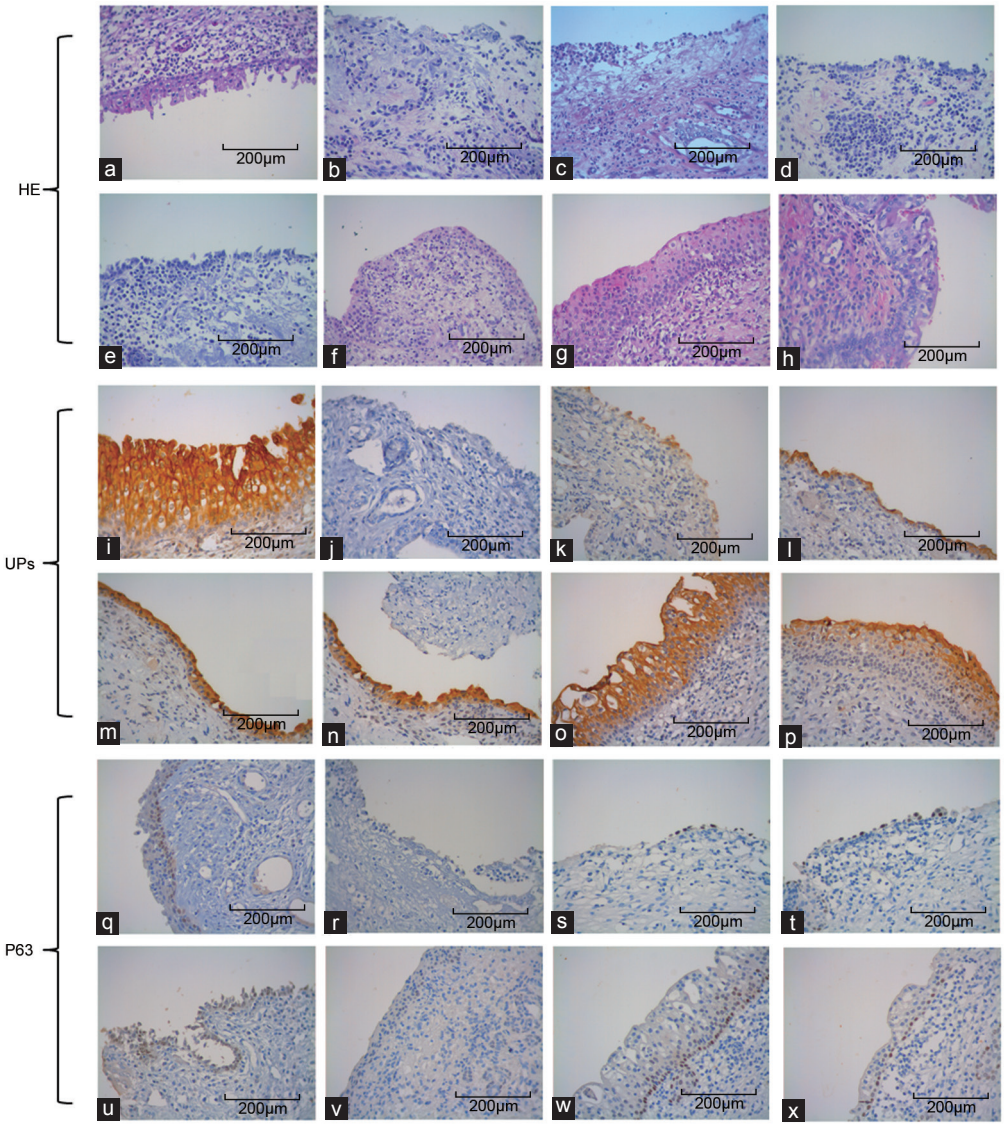

Figure 1: Epithelium of the prostatic urethra by H and E staining and expression levels of Ups and p63 in urotheliums of the prostatic urethra (×400). (**a**) Preoperative epithelium of the prostatic urethra by H and E staining; (**b**) 3 days after TmLRP by H and E staining; (**c**) 5 days after TmLRP by H and E staining; (**d**) 7 days after TmLRP by H and E staining; (**e**) 10 days after TmLRP by H and E staining; (**f**) 2 weeks after TmLRP by H and E staining; (**g**) 4 weeks after TmLRP by H and E staining; (**h**) 8 weeks after TmLRP by H and E staining; (**i**) expression levels of Ups in preoperative epithelium of the prostatic urethra; expression levels of Ups in 3 (**j**), 5 (**k**), 7 (**l**), 10 (**m**) days, 2 weeks (**n**), 4 weeks (**o**), 8 weeks (**p**) after TmLRP; (**q**) expression levels of p63 in preoperative epithelium of the prostatic urethra; expression levels of p63 in 3 (**r**), 5 (**s**), 7 (**t**), 10 (**u**) days, 2 weeks (**v**), 4 weeks (**w**), 8 weeks (**x**) after TmLRP.

nature formed from 2 to 8 weeks, which were generally UPs positive, particularly in the umbrella cell layers (**Figure 1n–1p**).

Compared with normal specimens (**Figure 1q**), there were no p63-positive cells in the wounds at day 3 (**Figure 1r**). However, scattered p63-positive cells were visible at day 5 (**Figure 1s**). p63-positive cells were insularly distributed and associated with cells of the remaining prostatic tissue, which also expressed p63 protein at day 7 (**Figure 1t**). At day 10, insular cell clusters developed a continuous monolayer covering the surface of the wound (**Figure 1u**). Two weeks after surgery, a basal cell layer formed in the newly developed urothelium and the basal cells displayed p63-protein expression (**Figure 1v**). p63-positive basal cells were continuous and an integral part of the basal layer of the well-differentiated newly formed urothelium 8 weeks after surgery (**Figure 1w** and **1x**).

Re-epithelialization is the key to the healing process of the prostatic urethra after TURP in patients with BPH. During the whole healing process in the present study, we found no evidence of epithelial migration from the bladder neck or proximal end of verumontanum to the wounds. These results suggest that re-epithelialization may not occur by migration of epithelia from the bladder neck or proximal end of the verumontanum, rather the remaining prostatic tissues may be an important cellular source for the re-epithelialization of the prostatic urethra. Also, our results suggested that p63-positive basal cells in the remaining prostatic tissues may participate in the re-epithelialization process of the prostatic urethra.

AUTHOR CONTRIBUTIONS

LL, HL and GHL conceived the study, established the design, and performed the experimental work. SJX and JL participated in the establishment of the canine model. XSY participated in the immunohistochemistry work. YDW and ZLS participated in the data

analysis and provided critical comments on the study design and manuscript. LL drafted this manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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