Urological Survey

histologically. Some authors suggested that the hyperplastic nodules in the PZ might be exophytic BPH in the TZ or the migration of ectopic TZ tissue into the PZ. The authors of the present study speculate that it is more likely that the hyperplastic nodules might originate from the PZ.

In the present study, the epithelial, stromal and luminal composition of the tissue was determined using a computer-assisted quantitative morphometric analysis method in biopsy specimens obtained from patients with PZ or TZ hypoechoic nodules on transrectal ultrasound, and that were histologically confirmed as BPH. The incidence of apoptosis and cell proliferation was analyzed comparatively in these hypoechoic nodules according to the zonal location. The authors also examined the relative expression of proteins involved in the regulation of prostate proliferation and apoptosis: (i) epidermal growth factor receptor (EGFR), which is in the signal transduction pathway that participates in the mediation of cell growth and has been implicated in prostatic epithelia cell proliferation in vitro; (ii) TGFβ1, the most extensively studied negative growth factor. The predominant effect of TGFβ1 on growth in vivo and in vitro is inhibition of cell proliferation; (iii) bcl-2, a potent apoptosis suppressor; and (iv) androgen receptor (AR); steroid binding to AR could stimulate proliferation and differentiation of epithelial cells and inhibit prostate cell apoptosis.

The results of the present study showed that no apoptotic cells were detectable in stroma, which indicated stromal growth due to cell proliferation, in the absence of cell death. The authors discussed that recent studies reported that the cell apoptotic rate in different regions of the ductal system is different, apoptosis being much less in the proximal ends. The proximal and distal regions of the ductal system correspond to the TZ and PZ of the human prostate. The present results showed that the cell apoptotic rate in the epithelium was much higher in PZ than in TZ hyperplastic nodules, which was in concordance with the higher TGF 1 and lower bcl-2 expression in the epithelium of PZ than TZ hyperplastic nodules. In the present study, TGFβ1 staining was intense in the epithelial cells, and bcl-2 expression was consistently restricted to the basal cell layer. This might explains why no apoptotic cells were detectable in the stroma of PZ and TZ hyperplastic nodules.

So, the authors concluded that the present results indicate that some hyperplastic nodules in the PZ might originate from the PZ, and the formation of these nodules might be modulated in a different way to that in the TZ.

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RECONSTRUCTIVE UROLOGY

Terminal urothelium differentiation of engineered neoureter after in vivo maturation in the “omentum bioreactor”
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Objective: Long ureteric defects may theoretically be repaired with the use of tissue-engineered neoureter. However, attempts to construct such a neoureter in animal models have failed because of major inflammatory response. Avoidance of such inflammation requires a well-differentiated urothelium. We investigated whether omental maturation of a seeded construct in a pig model could achieve terminal differentiation of the urothelium to allow construction of a stricture-free neoureter.
Material and Method: Bladder biopsies were taken to allow urothelial and smooth muscle cell cultures. These cultured cells were used to seed small intestinal submucosa (SIS) matrix. After 2 wk of cell growth, the in vitro SIS-seeded construct was shaped around a silicone drain and wrapped by the omentum to obtain neoureters. These neoureters were left in the omentum without any contact with urine, and then harvested 3 wk later for histologic and immunohistochemical studies. 

Results: Before implantation, the in vitro constructs were composed of a mono- or bilayer of undifferentiated urothelium overlying a monolayer of smooth muscle cells. After 3 wk of omental maturation, these constructs were vascularized and comprised a terminally differentiated multilayered urothelium with umbrella cells over connective tissue and smooth muscle cells, with no evidence of fibrosis or inflammation.

Conclusion: We obtained, for the first time, with this model of in vivo maturation in the omentum, a mature neoureter composed of a well-differentiated multilayered urothelium.

Editorial Comment

The anatomy and structure of the ureter is still not completely understood. Because of its embryonic development the blood supply restricts the reconstructive possibilities. Over a decade researchers look into the option to find a better substitute of a ureter than the common used ilium interproximat (1). With the improvement of Mitrofanoff the diameter of the segment was adjusted but still complications are seen although the needed length of ileum was significantly reduced and the resorption reduced (2).

Baumert et al. (3) present impressively a “sandwich model” with differentiated urothelium and a single layer of smooth muscle cells on SIS® different to others (4).

During the recent years researchers presented remarkable results demonstrating the progress tissue engineering (5). One important lesson, even known in the reconstructive surgery prior, was the need of the optimized nutrition of the in vitro created tissue. Atala et al. reported an optimized outcome of the clinical used in vitro pre-seeded scaffold for bladder reconstruction with an omental flap wrapping (6).

On the one hand the presented indication of a neo-ureter using an omentum flap makes the created ureter even more maneuverable compared to the possible “short” mesenterium of the ileum interproximat. On the other hand, Dahms et al. (7) published 10 years ago the ureter replacement by an acellular matrix, which was regenerated by urothelium and smooth muscle cells and functional, but in the following study in the rodent as well in the large animal model the created ureter shrunk after the stent removal although the prior seen urothelium lining was present (data not published). Some might argue that the presented approach will prevent the shrinking but as the author state it needs to be proven. Because others have made similar experiences - probably only a minority is published - it should be considered to report the outcome of an extended follow-up after the stent removal and as a replacement for a ureter.

References


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A quantitative method for evaluating the degradation of biologic scaffold materials
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Scaffolds derived from naturally occurring extracellular matrix (ECM) have found extensive use in the fields of tissue engineering and regenerative medicine. Many of these scaffolds are designed to degrade rapidly as they are replaced by new host tissue. Other scaffolds are chemically crosslinked to slow the rate of degradation or add strength to the scaffold. Commercially available ECM scaffolds have considerable variability with regards to tissue origin and methods of processing, and little is known about their rate of degradation and the fate of their degradation products. A novel method is described herein to integrally label ECM with a radioactive isotope ((14)C). It was found that a number of tissues are efficiently labeled, including heart, liver, trachea, pancreas, small intestine, and urinary bladder tissue. Of the tissues analyzed, only spleen was not found to contain detectable levels of (14)C. The technique is extremely sensitive, accurate, and safe, but requires access to accelerator mass spectrometry, and is expensive and time consuming. This model represents the first described quantitative method to determine the rate of degradation for an ECM scaffold and to track the fate of the degradation products.

Immune response to biologic scaffold materials
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Biologic scaffold materials composed of mammalian extracellular matrix are commonly used in regenerative medicine and in surgical procedures for the reconstruction of numerous tissue and organs. These biologic materials are typically allogeneic or xenogeneic in origin and are derived from tissues such as small intestine, urinary bladder, dermis, and pericardium. The innate and acquired host immune response to these biologic materials and the effect of the immune response upon downstream remodeling events has been largely unexplored. Variables that affect the host response include manufacturing processes, the rate of scaffold degradation, and the presence of cross species antigens. This manuscript provides an overview of studies that have evaluated the immune response to biologic scaffold materials and variables that affect this response.

Editorial Comment
Biologic scaffold materials in the currently available form are unsatisfactory for reconstruction of the lower urinary tract. They are to some extend an obstacle to vascularization and re-innervation of the reconstructed
segment, but they also lead to a reaction of intact surrounding tissue due to a normal immune and inflammatory response. In the two papers selected here, the authors have tried to develop a model for a quantitative determination of the degradation process and the tracking of extracellular matrix used as scaffold for urinary bladder reconstruction, for example. Furthermore the host response which is or maybe responsible for scaffold degradation has been worked up. These data are very important and very timely because due to the problems with artificial matrix acellular derived from human or animal sources are currently the most commonly used materials in tissue engineering for clinical purposes.

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NEUROUROLOGY & FEMALE UROLOGY

State of the art of where we are at using stem cells for stress urinary incontinence
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Aims: This review aims to discuss: 1) the neurophysiology, highlighting the importance of the middle urethra, and treatment of stress urinary incontinence (SUI); 2) current injectable cell sources for minimally-invasive treatment; and 3) the potential of muscle-derived stem cells (MDSCs) for the delivery of neurotrophic factors.

Methods: A PUB-MED search was conducted using combinations of heading terms: urinary incontinence, urethral sphincter, stem cells, muscle, adipose, neurotrophins. In addition, we will update the recent work from our laboratory.

Results: In anatomical and functional studies of human and animal urethra, the middle urethra containing rhabdosphincter, is critical for maintaining continence. Cell-based therapies are most often associated with the use of autologous multipotent stem cells, such as the bone marrow stromal cells. However, harvesting bone marrow stromal stem cells is difficult, painful, and may yield low numbers of stem cells upon processing. In contrast, alternative autologous adult stem cells such as MDSCs and adipose-derived stem cells can be easily obtained in large quantities and with minimal discomfort. Not all cellular therapies are the same, as demonstrated by the differences in safety and efficacy from muscle-sourced MDSCs versus myoblasts versus fibroblasts.

Conclusions: Transplanted stem cells may have the ability to undergo self-renewal and multipotent differentiation, leading to sphincter regeneration. In addition, such cells may release, or be engineered to release, neurotrophins with subsequent paracrine recruitment of endogenous host cells to concomitantly promote a regenerative response of nerve-integrated muscle. The dawn of a new paradigm in the treatment of SUI may be near.

Editorial Comment

The authors describe the current status of research into using stem cell therapy for stress urinary incontinence. This is an excellent read for those who wish to gaze through the looking glass into the future of urology. The last paragraph of the Introduction section alone is worth reading and looking back upon in one or