SEXUAL MEDICINE REVIEWS

Urinary Tissue Engineering: Challenges and Opportunities

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ABSTRACT

Introduction: In this review, we discuss major advancements and common challenges in constructing and regenerating a neo-urinary conduit (NUC). First, we focus on the need for regenerating the urothelium, the hallmark the urine barrier, unique to urinary tissues. Second, we focus on clinically feasible scaffolds based on decellularized matrices and molded collagen that are currently of great research interest.

Aim: To discuss the major advancements in constructing a tissue-engineered NUC (TE-NUC) and the challenges involved in their successful clinical translation.

Methods: A comprehensive search of peer-reviewed literature from PubMed and Google Scholar on subjects related to urothelium regeneration, decellularized tissue matrices, and collagen scaffolds was conducted.

Main Outcome Measure: We evaluated the main biological and mechanical functions of urinary tissues, the need for TE implants to create a urinary diversion, the reasons for their failures in clinical settings, and the applications of decellularized tissue matrices and collagen-based molded scaffolds in their regeneration.

Results: It is necessary to create a urine barrier that prevents urine leakage into the stroma that can cause failure of the graft. Despite the regeneration potential of the urothelium, the limited supply of healthy urothelial cells in patients with bladder cancer remains a major challenge. In this context, alternative strategies, such as transdifferentiation of cells into urothelium or engineered scaffolds based on decellularized tissues and molded collagen with robust urine barrier properties, are active areas of research.

Conclusion: There is an immediate need for developing a functional TE-NUC that can improve the quality of life of patients with bladder cancer. It is possible to achieve a TE-NUC by bioengineering an implant that has appropriate biological and mechanical properties to store and transport urine. We anticipate that future advancements in urothelium regeneration and material design will lead us closer to successful neo-urinary tissue constructs. **Singh A, Bivalacqua TJ, Sopko N. Urinary Tissue Engineering: Challenges and Opportunities. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Tissue Engineering; Urothelium; Acellular Matrices; Collagen; Scaffolds; Urinary Bladder; Ureter; Urethra; Neo-Urinary Conduit

INTRODUCTION

Urinary tissues are primarily responsible for the storage and transportation of urine after filtration from the kidney. The bladder acts primarily as a reservoir for urine storage, and the ureters and urethra act as passageways for urine transport. The bladder's unique repetitive expansion and contraction capabilities combined with a tight urine barrier and overall strength to withstand urine pressure make it a very complex organ.[1] Although somewhat less complicated, the ureters and urethra have similar bio-structural and functional properties. These tissues are under fluid shear stress and radial pressure owing to urine storage and transport. Furthermore, these tissues have an inner multilayer epithelial lining, the urothelium, which protects the stroma from urine (Figure 1A–C). Compared with the ureter and urethra, the bladder urothelium functions in a more complex biodynamic environment of significant repetitive contraction and expansion for the expulsion and storage of urine. Therefore, overall, the concepts of ureter and urethra regeneration can be considered an extension and simplified version of bladder regeneration.

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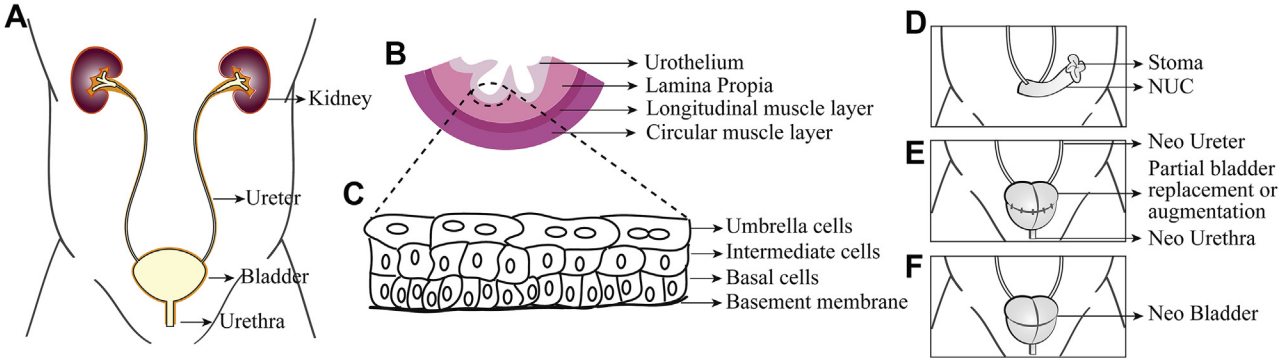

Figure 1. Panel A shows schematics of native urinary tissues and organs. Panel B shows native urinary tissues and organs in a layer-by-layer arrangement. Panel C shows typical epithelium in the proximal urethra, ureter, and bladder. Panel D shows tissue-engineering approach to construct the neo-urinary conduit. Panel E shows tissue-engineering approach to construct the neo-ureter, neo-urethra, and partial bladder replacement or bladder augmentation. Panel F shows tissue-engineering approach to construct the neobladder.

Reconstruction and regeneration of urinary tissues are needed to correct some functional abnormalities or disease conditions.[2] For example, urinary diversion (Figure 1D) is required in patients with bladder cancer who undergo radical cystectomy (complete removal of the bladder). There are several surgical approaches to urinary diversion. An ileal conduit is the simplest and most commonly performed technique.[3] It requires removing a segment of the patient's small intestine from the gastrointestinal (GI) tract.[4] However, this approach is prone to many health complications, including metabolic disturbances, stone formation, urine leakage, and chronic infections owing to the inherent absorptive and secretory properties of GI segments and renal compromise with the early development of chronic kidney disease.[5–10] To potentially minimize or eliminate some of these challenges, tissue-engineering (TE) approaches with biomaterials with or without seeded tissue-specific cells or stem cells have been investigated.[11–21] These studies have reported enhanced and accelerated partial tissue defect regeneration and healing, which have greatly contributed to our understanding of urologic tissue repair, augmentation, and replacement (Figure 1D–F). Unfortunately, their clinical translations are limited[11] or unsuccessful because of insufficient mechanical design and properties or inadequate functional biological responses, such as an insufficient urine barrier and contractibility, lack of vascularization, antifibrosis properties, and the limited availability of healthy autologous cells.[2,13] Nevertheless, bioengineered urinary tissues can help improve the quality of life of thousands of patients, including those with bladder cancer, who are in desperate need of tissue replacement owing to various health conditions, trauma, and diseases.

TE approaches often require scaffolds to provide guiding and structural platforms for mature, differentiated, or stem cells to regenerate tissues. Scaffolds can be implanted to the repair site with or without cells. Unseeded scaffold technologies depend on the body's natural physiologic remodeling response and the biocompatibility and biodegradability of the scaffold materials that are custom designed for facilitating tissue integration. These scaffolds are infiltrated with host cells that remodel and ideally replace the scaffold over time with target tissues. This method is simple, requires less preoperative preparation, and can take less surgical time. However, it can result in graft shrinkage, poor target tissue replacement, and uncontrolled and fibrotic tissue formation.[22,23] Studies have shown that pre-seeding the scaffolds with cells can mitigate some of these negative outcomes, such as graft shrinkage.[22,23] However, this process requires additional preparatory steps of cell harvesting, isolation, seeding, and proliferation on scaffolds. Tissue remodeling is an outcome that depends on macrophage-based processes and phenotypes (named M1 and M2) important for wound healing and tissue regeneration.[24] Any imbalance in the remodeling process can lead to regeneration of neo-tissues with properties that differ from the host tissues and lead to uncontrolled deposition of extracellular matrices (ECMs), leading to the development of fibrotic tissues.[25] The fate of these implants also depends on the size of the neo-tissues to be regenerated, the materials' mechanical properties, and their abilities to allow cell infiltration and promote neovascularization.[16,24,26] Although it is difficult and rare to find all these favorable characteristics in a single graft, tissue engineers continue to develop sophisticated cell-instructive scaffold technologies that might solve the major challenges in urinary tissue engineering in the near future. In subsequent sections, we discuss the advancements, challenges, and opportunities in the construction of neo-urinary tissues. Specifically, we focus on urothelium regeneration and scaffolds that have shown promise in constructing these tissues.

MAJOR CHALLENGES AND RESEARCH OPPORTUNITIES

Not surprisingly, some major challenges are not related to the target urinary tissues to be replaced. For example, pre-seeding constructs has been shown to be beneficial for replacement of urethral, ureteral, or bladder tissues. Direct implantation of acellular constructs for bladder reconstruction leads to graft