Journal of Tissues and Materials 2018 1(1): 18-24

Journal homepage: www.jourtm.com

Tissue Engineering in Lower Urinary Tract Reconstruction

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Received: 01 June 2018, Accepted: 14 June 2018

Abstract

Urology diseases and disorders are often diagnosable by special clinical symptoms. Congenital disorders, iatrogenic injuries, inflammatory diseases, infections, tumors, cancers and other conditions of the genitourinary system are in this category. The treatment of these disorders usually involve classical surgeries including organ transplant from deceased or other methods, which are associated with transplant - related side effects and complications. Tissue engineering is a rapidly expanding, promising field which addresses tissue and organ failure and organ reconstruction. A myriad of Clinical and preclinical studies have been conducted on different treatment methods and tissue engineering in the field of urology, which have been reviewed in our present study.

Keywords: Urology, Tissue Engineering, Regenerative medicine

1. Introduction

Tissue engineering is a rapidly expanding, promising field which addresses fabrication of biological substitutes to rehabilitate and reconstruct damaged tissues and organs (1). Tissue engineering has four main components which are necessary to achieve optimal outcomes. These components include stem cells, growth factors, scaffold or appropriate extracellular matrix and finally a proper blood flow to supply oxygen and nutrients. The source of tissue utilized can be autologous (same individual), allogeneic (same species, different individual) or heterologous (different species). Using autologous cells and tissues gives excellent results in tissue engineering because of the lower association with immune complications, thus, minimizing the risk of tissue rejection (2). The Final goal of tissue engineering and regenerative medicine is organ reconstruction. Congenital disorders, iatrogenic injuries, inflammatory diseases, infections, tumors, cancers and other conditions of the genitourinary system may lead to organ failure or inadequate function. In the past two decades, a lot of experimental and clinical studies have been performed on genitourinary system, which have restored both the lower and the upper urinary tract (3–6). Tissue engineering has been taken into great consideration because of its potential in treating diseases and regenerating damaged tissues. Although Particularly in urology numerous articles have been published through several years, there is still a long way to rectify the problems and treat diseases optimally. Researchers are investigating tissue engineering protocols to achieve potential therapeutic benefits in urology. Recent investigations have studied the use of prepuce as a scaffold possessing excellent physical properties for Bladder Muscular Wall and urethral reconstruction. Reconstruction of bladder's wall with cholecyst-derived extracellular matrix has also obtained promising results (7–9). the purpose of this article is to review the latest clinical applications of tissue engineering in the field of urology.

1. Biomaterials and Tissue sources

1.1. Bladder

Bladder tissue engineering is a significant research in urology. In many cases of acquired or congenital disorders such as bladder exstrophy, myelomeningocele, lumbar traumas, Intestinal cystitis and infections, augmentation of the bladder is necessary (10). Replacement of urinary tracts with intestinal segments are followed by further complications such as mocusa over production, urolithiasis and malignancy (2). Chronic contact of urine with gastrointestinal epithelium causes side effects and induces long-term risks. Recent preclinical and experimental studies are trying to find reasonable ways.

Currently available material for bladder reconstruction are classified as natural derived and synthetic:

Collagen is a one of the main materials which are sued in tissue engineering of bladder (11). As well as alginate is a biomaterial which recently used in bladder tissue engineering (12). Alongside of the natural materials, synthetic material plays crucial role in tissue engineering. Many synthetic materials like PLGA(13), PCL(14), silicon, polyurethane (15) and PGA (16) were used to find the appropriate material for replacement and restoration of the bladder. However, due to functional and biocompability problems these efforts faced failure and difficulties, such as urolithiasis, recurrent urinary tract infections and implant rejection (17,18). Thus, research on finding new techniques in urology is ongoing.

Recent studies demonstrate that some materials and technics with better biocompatibility and mechanical strength and also the ability to stand in a tridimensional framework (same as bladder) are suitable for bladder reconstruction (19,20). Talab et al (21) in their study showed that autologous smooth muscle cell sheet in scaffold-less tissue engineering has a good capability in cycstoplasty. Several studies have demonstrated Cholecyst-drived extra cellular matrix as a natural and collagen rich scaffold with proper mechanical features, making it useful in tissue engineering (22,23) Moreover, it has been proved that implantation of Cholecyst-drived extra cellular matrix is not followed by chronic inflammation (24).

Kajbazadeh et al (7) demonstrated that autologous fragment-seeded CDECM, as a natural collagen based scaffold, is an appropriate material for bladder augmentation. They evaluated biocompatibility, clinical and histological characteristics between two groups (CDECM seeded with autologous detrusor muscles small fragments (ADMSF), and CDECM alone). As a result, they exhibited that decellularized process did not affect the integrity of ECM structure and no degradation in collagen was detected. The SEM analysis certified the preservation of the ECM structure of decellularized issues compared to the original ones. In addition, there were no signs of rejection, weight or appetite loss and fever in different samples, which proves the potentiality of Decellularized CDECM as a scaffold with less antigenic features (7) contrary to other studies (25,26). This study demonstrates that by using this new technic, restoration of bladder is possible in 24 weeks.

1.2. Urethra

Urethral reconstruction is a main challenge for urologists. Adjacent to the corpora cavernosa is the corpus spongiosum on the ventrum of the penis, traversed by the anterior urethra starting at the perineal membrane. This conduit allows urine flow from bladder. Stratified epithelium and pseudostratified columnar epithelium covers the proximal part and stratified squamous epithelium covers the distal part of the urethra, the epithelium is surrounded by smooth muscle. The urethra is the next most evident tissue used for reconstruction in patients with deficient or poor-quality native tissue such as congenital proximal hypospadias or patients with primary or recurrent urethral stricture disease. Congenital and acquired events could defect Urethra, common causes of urethral defects are congenital deformities, traumas, inflammation, and cancer. Hypospadiasis is one of the most common genitourinary disorders in United States with prevalence of 1 from every 300 live male births in each year (27). Hypospadias is the abnormal location of the urethra on the ventral surface of the penis shaft which is likely to be associated with aborted development of the urethral spongiosum, ventral prepuce, and penile chordee. Urethral loss and Fistula formation, as the most common complications after failed hypospadias surgery, still remain as a challenge. Although several techniques have been innovated to prevent and treat these complications, urethro-cutaneous fistula has still remained as a concern (28).

Pre-clinical studies regarding urethral repair and replacement in animal models has shown significant results. The size of the defect is the most challenging variable in these studies which involves simple hypospadisis to complete urethra repair.

Some studies (29,30) have reported successful repair of urethral defects in rabbit models for 1 centimeter lenght defects by employing unseeded biomaterial matrix, SIS, BAMG (Biodimentional anisotropic mesh generator).

In other studies, unseeded tubularized grafts were used to repair the urethra in short urethral defects and also defects with 1 centimeter, 1.5 centimeters and 6 centimeters length, these studies showed various results and success rates.

Sievert et al (31) succeeded to repair urethral defects up to 1centimeter using BAMG and acellular dermal matrix in rabbit models. Recent studies indicate that as the defect size expands, the rate of success decreases. Adding other components is necessary to increase the chance of success.

Utilizing unseeded tube grafts in defects with the sizes of 1 to 1.5 centimeters, shows lower success in comparison with cell-seeded component in the same scaffolds (32,33).

Dorin at el (34) conducted a study to find the maximum potential distance for normal native tissue regeneration over a wide range of distances performed as an experimental model for tubular grafts. In this study Tubularized urethropalsties were performed on rabbit models by employing acellular matrices of bladder submucosa at different lengths of 0.5cm, 1cm, 2cm and 3 centimeters. Urethrography was performed within first, third and fourth weeks. 0.5cm was reported as the maximum defect distance suitable for normal tissue regeneration by acellular grafts relying on native cells. These studies demonstrate the important role of utilizing cells and effective component (growth factors and cell signaling) in graft acceptance.

The next important variable is the type of scaffold and matrix used in the process. Proper cell-seeding is a necessary component for the scaffold used. Several studies have been performed to use natural body tissue such as preputial, buccal mucosa, small intestinal submucosa and amniotic membrane, instead of polymers (8,30,33,35).

Fibrin sealant has been used frequently in urethroplasty (36,37). the main reasons making it useful are local hemostatis features and Adherence abilities.

Researchers in an animal model study tried to repair Hypospadiasis by the combination of two new techniques including acellular matrix and fibrin glue. The results expressed that mice treated with acellular matrix and fibrin glue had a significant improvement in comparison with those repaired with acellular matrix alone. Moreover, in acellular matrix and fibrin glue group angiogenesis was amplified although it was not significant (8).

Recently, researcher used 3D bioprinting technology to fabricate cell-laden urethra. Zhang et al (38) used PCL/PLCL blend and dual autologous cells in fibrin hydrogel to investigate biomimetic mechanical and cell growth in in-vivo environment.

1.3. Penis

In Tissue engineering, several efforts have been done in order to repair and reconstruct phallus structural disorders. Various investigations have been conducted on animal and human subjects. several studies have been done regarding application of stem cells seeded in collagen matrix and fabrication of tissue scaffolds accompanied with various cells, in order to reconstruct penile function (39,40).

ZHE JIN et al (41) performed a study on 80 patients with small penis syndrome (SPS) to investigate the safety and efficacy of a poly acid-co-glycolide biodegradable scaffold coated by autologous fibroblasts for penile girth enlargement. Postoperative follow up showed significant increase in mean penile girth. A study conducted in 2012, provided strong experimental evidence for the functionality and feasibility of tunica albuginea reconstruct. In the study, autologous fibroblast seeded on a polyglycolic acid (PGA) scaffold were utilized for tunica albuginea reconstruction in Sprague Dawley adult male rats (42).

Overall, penile reconstruction has had a significant improvement during the previous years.

2. Conclusion

Tissue engineering has witnessed an impressive growth in the recent years, yet it faces lots of problems and challenges. These challenges are often related to the complexities resulted from regenerative and recovery mechanisms of the body. Despite these problems, there are great options for revolutionizing the reconstructive options in these patients. Recent studies on Cholecyst-drived extra cellular matrix has shown good results. Recent research and experiments show that tissue engineering in urology is growing considerably and although clinical studies are still at an early phase, a great potential for improvement of the treatment results exist.

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