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Biomatrices in Urethral Reconstruction

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Abstract

Urethral reconstruction is still a big challenge in urology. Traditionally, the penile skin or buccal mucosa was used as graft for replacement. However, the morbidity of the donor site was reported previously. Furthermore, there is a lack of an adequate autologous donor graft in many cases. The tissue engineered urethra may provide an alternative to the reconstruction. Herein, we reviewed the biomatrices for urethral substitution either in animal model or in clinical cases.

Keywords: Urethral reconstruction; Biomaterials; Urethral stricture

Introduction

Various urethral disorders, such as hypospadias, stricture, require surgical reconstruction [1-3]. The most commonly used sources of graft were penile skin or buccal mucosa [4-7]. However, in many circumstances, an adequate amount of those tissues was not available. In addition, a number of surgical complications were described in previous studies, including prolapse and stricture recurrence [8-10]. Furthermore, bothersome donor site morbidity was associated with buccal mucosa, such as pain, numbness, ulceration and difficulty in opening mouth [11]. Penile skins also have the potential risk of subcutaneous bleeding, infection and the dorsal nerve injury [12].

Recently, the development of regenerative medicine provided novel biomaterials for urethral reconstruction, including natural decellularized matrix, protein derived scaffolds and synthetic polymers. The modification of those materials, such as oxidation with 5% peracetic acid (PAA) or stretch in 90% ethanol, further improves their microstructure and biocompatibility. Herein, we reviewed biomaterials for urethral replacement in brief.

Natural Collagen Based Matrices

The natural collagen based matrices were derived from decellularized heterogenic tissue, including small intestinal submucosa (SIS) [13-15], bladder accellular matrix (BAM) [16-18], accellular corpus spongiosum matrix (ACSM) [19] and accellular dermal matrix (ADM) [20]. Bhargava et al. [20] firstly used ADM and oral cells to fabricate tissue engineered buccal mucosa to repair long complex urethral stricture in 5 patients, the urethra successfully regenerated in 3 of them and maintained functional at mean follow-up of 8 years, however, 2 of them resulted in complete or partial graft removal. Such natural collagen based material for urethral reconstruction was far from ideal. Although the accellular matrix contains biological molecules beneficial for cell growth, there are two main disadvantages that limit further application. One of them is the high density of the material that prevents the transport of nutrient, air and metabolic substance. Another one is the retained heterogenic nuclear components which lead to chronic inflammation, fibrosis and calcification [21, 22].

Liu et al. [21] and Wu et al. [22] reported that 5% paracetic acid (PAA) treated SIS and BAM increased the porosity of the fresh SIS, decreased the heterogenic cellular component, and prompted cell proliferation *in vitro* and in nude mice model. Initially, it was presumed that the maximum distance of the complete healing from the wound edge was 1 cm in a rabbit model [23]. However, Huang et al. [24] demonstrated that unseeded 5% PAA modified BAM could repair long urethral defect (1.5 × 0.8 cm^2). In our previous study, we found that 5% PAA treated SIS increased porosity and prompted cell proliferation. In addition, such modified SIS seeded with cells can repair larger urethral defect (1.7 × 1 cm^2, Figure 1), the urothelium, smooth muscle and vessel regenerated completely, however, fistula or stricture occurred in unseeded SIS or cell seeded non PAA treated SIS group [25]. Therefore, we considered that cell seeded scaffold and 3-dimension porous microstructure are two important factors to prompt tissue regeneration for large urethral defect.

Protein Derived Scaffolds and Cellulose

Silk fibroin (SF) is a novel protein obtained from *Bombyx mori* cocoons that have good biocompatibility and low immunogenicity [26,27]. The mechanical property and microstructure of was improved after it was stretched in 90% ethanol [28]. Both accellular and cell seeded SF showed good efficacy in urethral reconstruction in animal model [26,29,30]. Recently, Lv et al. [31] reported a novel oxygen-generating material composed of SF, keratin, calcium peroxide and gelatin. This study showed 3D porous structure, high mechanical property and steady release of oxygen, which improved the urethral tissue regeneration in dogs. There were two novel modified scaffolds using collagen-binding

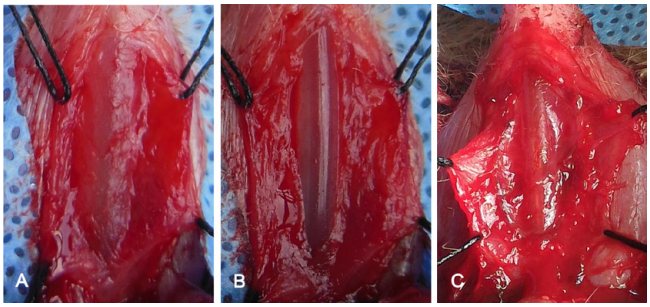

Figure 1: Urethral reconstruction procedure. A) The urethral mucosa was exposed; B) Penile mucosa was excised; C) The graft was sutured to the wound edge.

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VEGF or collagen/poly (L-lactide-co-caprolactone)-binding Wnt signal inhibitor for urethral reconstruction, both of them showed good efficacy in urethral reconstruction in an animal model [32].

Bacterial cellulose (BC) is obtained from *Acetobacter xylinum*, it has satisfactory mechanical property, nanostructure and biocompatibility [33]. However, its compact density limits its further clinical application. Huang et al reported that 3D porous structure of BC was formed following the treatment of gelatin, but the mechanical property was still maintained, with the mean tensile strength from 30.45 ± 6.78 Mpa to 16.6 ± 2.47 Mpa. Such modified BC enhanced cell proliferation *in vitro* and also prompted urethral epithelium, smooth muscle, vessel regeneration in an animal model [34].

Synthetic Polymer

Synthetic polymer materials were once used commonly, such as PGA, PLGA and the compound of PGA:PLGA [35,36]. They avoid potential heterogenic pathogen infection, and have ideal fiber diameter [19]. Raya-Rivera et al. [36] reported that urothelial cell seeded in PGA:PLGA successfully repaired complex urethral stricture in 5 children. The urethrography and flow rate demonstrated the tissue engineered urethra demonstrated wide caliber and satisfactory voiding function. However, the synthetic polymer has poor biocompatibility, and lacks adequate bioactive molecules for cell growth. In addition, it was reported that the degraded substances of the synthetic polymers caused chronic immunogenicity, and development of fibrosis in long term follow up [37].

Conclusion and Future Directions

Compared to traditional non modified biomaterials for urethral reconstruction, the novel biomaterials generally have higher porosity and better histocompatibility. However, the procedure of fabricating such novel materials for urethral replacement is relatively more complicated, including oxidation with 5% PAA and biological molecules binding scaffolds and electrospun biomaterials.

Reconstruction of the urethra is one of the biggest challenges in urology, especially for those patients with long complex extensive fibrosis and stricture. The vascular bed was destroyed in most cases, so the ideal scaffold should be equipped with degradable 3D porous structure to transport the nutrient to the new tissue, exhibit least immunogenicity and can promote neovascularization. Besides, it should also have suitable mechanical property because of the elastic nature of the corpus spongisum. Future studies should be conducted to find the most suitable biomaterials for the urethral reconstruction before its widespread clinical application.

Since the stricture recurrence in clinical cases is relatively high, the underlying mechanisms for the recurrence need to be clarified. The animal models that imitate the urethral stricture in clinical cases should be constructed for further study of the efficacy of different materials in urethral replacement.

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