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Advances in Tissue Engineering for the Treatment of Urethral Stricture

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Abstract: ***Urethral stricture is a common disease of the urinary system, mainly caused by trauma, inflammation, iatrogenic injury and other factors, which can lead to dysuria, urinary retention and even renal function impairment, seriously affecting the quality of life of patients. Traditional treatments such as urethral dilatation and urethroplasty have limitations, including a high recurrence rate, many complications, and a lack of graft. Recent rapid development in tissue engineering techniques has provided a new direction for the repair of urethral strictures. This review summarizes the progress of tissue engineering in the treatment of urethral strictures, including the application of scaffold materials, seed cells, bioactive factors, and explores the challenges and prospects of future development.***

Keywords: Urethral stricture, Tissue engineering, Stent material, Seed cells.

1. Introduction

Urethral stricture is a pathological condition of abnormal narrowing of the urethral lumen, and the incidence is significantly higher in men than in women. Its etiology is complex, including congenital malformation, trauma (such as riding span injury, pelvic fracture), chronic inflammation (such as lymphorrhea, tuberculosis), and iatrogenic injury (such as catheter insertion) [1,2]. Traditional treatment methods such as urethral dilatation and urethroplasty have problems such as high post-operative restenosis rate, many complications and lack of graft, and some patients need multiple surgeries, which seriously affects the quality of life of patients [3].

Recently, tissue engineering, as an emerging therapeutic tool, aims to construct functional urethral tissues and realize the dual repair of anatomical structure and physiological function [4,5]. The use of synthetic tissue also reduces the morbidity of donor-site complications of the graft during urethroplasty [6]. In addition, the field has made significant progress in stent design, cell source, and clinical transformation, providing new ideas for the treatment of complex urethral strictures.

2. Traditional Treatment and Limitations of Urethral Strictures

2.1 Non-surgical Treatment

Non-surgical treatment of urethral stricture mainly includes urethral dilatation, medical therapy, and laser therapy. Urethral dilatation serves as the treatment of choice for mild urethral strictures through mechanical expansion of the stricture segment to improve micturition function. However, this method requires repeated operation and has a high recurrence rate [7]. In addition, drug treatments (e. g., antifibrotic agents) and laser therapy have limited efficacy and are usually only applicable to specific cases [8]. The effect of drug treatment is unstable, and it is difficult to fundamentally solve the problem of stenosis.

2.2 Surgical Treatment

Surgical treatment is the main treatment of moderate and severe urethral stricture, mainly including open surgery (such as urethral strictotomy, urethroplasty), etc [9]. Among them, urethroplasty is widely regarded as the "gold standard" for the treatment of complicated urethral strictures. By removing the stricture segment or reconstructing the urethral structure, the patient can significantly improve the urination function, and the short-term success rate of urethroplasty can reach 85% to 95% [10]. However, there are some limitations to surgical treatment. First, multiple complications may occur at the material site of the autologous tissue graft [11,12], The postoperative inflammatory response may lead to the restricture and affect the surgical effect [13]. Secondly, the long-segment stenosis greater than 2 cm has the deficiency of autologous tissue graft, and some patients have incomplete functional recovery, and still have abnormal urodynamics after surgery, which affects the quality of life. Therefore, in clinical practice needs to strictly grasp the surgical indications and strengthen the postoperative follow-up management.

3. Application of Tissue Engineering in the Treatment of Urethral Strictures

The application of tissue engineering in the treatment of urethral stricture is mainly achieved through the design and optimization of scaffold materials, the selection and amplification of seed cells, and the regulation of bioactive factors. The combination of these techniques offers new possibilities for the treatment of urethral strictures, significantly improving patient quality of life.

3.1 Design and Optimization of Stent Materials

The stent material is the core component of tissue engineering, and its design needs to meet the basic requirements of biocompatibility, degradability and mechanical adaptation. The ideal scaffold material needs not only to provide physical support for cell attachment and proliferation, but also to match the tissue regeneration process during degradation.

3.1.1 Natural materials

Natural materials have unique advantages in the repair of tissue engineering urethral strictures, especially acellular matrix (such as bladder submucosal matrix, small intestine submucosal matrix) because it retained natural extracellular matrix components (such as collagen, fibronectin and laminin), can provide a good microenvironment for host cells, promote cell migration, proliferation and angiogenesis. These components not only provide structural support for the cell, but also regulate the biological behavior of the cells through cell-matrix interactions, thereby promoting tissue regeneration. Studies have shown that the acellular matrix exhibits excellent biocompatibility and regenerative potential in urethral narrow tract repair [14]. Decellular matrix reduces immunogenicity by removing cellular components, while retaining the natural structure and biological activity of the extracellular matrix, making it an ideal scaffold material. Among them, the bladder submucosal matrix (BAMG) has been widely used in the repair of urethral stricture, which can support the regeneration of urothelium and smooth muscle [15]. BAMG not only provides a three-dimensional growth space for cells, but also promotes tissue regeneration and functional recovery through the release of bioactive molecules (such as growth factors and cytokines). In addition, the small intestinal submucosal matrix (SIS) is also a commonly used decellarized matrix material. Studies have shown that SIS can promote angiogenesis and tissue remodeling in the repair of urethral stenosis, significantly improving the repair effect [16]. The fibrous structure and bioactive components of SIS are able to guide the directed migration and differentiation of host cells, thus accelerating the regeneration process of urethral tissue.

3.1.2 Synthetic materials

Synthetic materials have important application value in the treatment of tissue-engineered urethral strictures, especially materials such as polycaprolactone, polylactic acid, polyglycolic acid and its copolymers have been widely studied for their regulated degradation rates, excellent mechanical properties and processibility. These materials are able to match the regeneration needs of different tissues by adjusting the molecular weight, crystallinity and copolymerization ratio, thus providing a flexible design space for urethral repair. However, the surfaces of synthetic materials often lack biological activity, which limits the ability of the cells to adhere, proliferate and differentiate. Therefore, surface modification techniques (e. g., coating, chemical modification, or physical treatment) have become a key strategy to improve the biocompatibility of synthetic materials. It has shown that cell affinity of synthetic materials can be significantly enhanced by surface modification. The methods of surface modification of synthetic polymers, including plasma treatment, chemical grafting and biomolecular coating, can effectively improve the surface properties of materials and promote cell adhesion and proliferation [17]. Bioactive molecules such as collagen, fibronectin, and laminin are used for surface modification of synthetic materials. In addition, hydrophilic groups (such as hydroxyl and carboxyl groups) can be introduced through plasma treatment or chemical grafting methods, which can also improve the surface wettability and cell compatibility of synthetic materials.

Although the surface modification technology significantly improves the bioactivity of synthetic materials, their stability and controllability in long-term applications still need to be further optimized. For example, the uniformity and durability of modified coatings, as well as the activity maintenance of biomolecules are the focus of current research. In addition, degradation products of synthetic materials (e. g., lactic and glycolic acids) may cause a local acidic environment that affecting cell behavior and tissue regeneration. Therefore, researchers are exploring regulating the release of degradation products by composite natural materials or the addition of buffers, to improve the biocompatibility of materials.

3.1.3 Composite Stent

Composite scaffolds show great potential in urethral stricture repair by combining the advantages of natural and synthetic materials. Synthetic materials have regulated mechanical properties and degradation rates but lack biological activity. By combining the advantages of the two, composite stents can not only provide good mechanical support, but also provide a suitable microenvironment for cells, thus significantly improving the effect of urethral repair. Collagen-polycaprolactone (PCL) composite scaffold is a typical composite scaffold material. Collagen, as the main component of natural extracellular matrix, can provide bioactivity signals for cells and promote cell migration and proliferation; PCL provides excellent mechanical strength and degradation control. Studies show that the collagen-PCL composite scaffolds exhibit good biocompatibility and regenerative potential [18]. This composite scaffold can not only support the adhesion and proliferation of urothelial cells and smooth muscle cells, but also gradually degrade in vivo, providing space for the formation of new tissue. The composite scaffolds of the acellular matrix with synthetic materials have also received much attention. This composite stent is able to promote angiogenesis and tissue remodeling, significantly improving the effect of urethral repair.

3.2 Selection and Amplification of Seed Cells

Seed cells are the key to the treatment of tissue-engineered urethral strictures, and they should be selected based on the characteristics of strong proliferation ability, high differentiation potential and low risk of immune rejection.

3.2.1 Autologous urothelial cells

Autologous urothelial cells are an ideal choice for the treatment of urethral strictures due to their ease of access and low risk of immune rejection. However, its limited source and weak in vitro amplification have limited its extensive application [19].

3.2.2 Mesenchymal stem cells

Mesenchymal stem cells can be isolated from bone marrow and adipose tissue, with multidirectional differentiation potential and potent paracrine effects. Mesenchymal stem cells can not only differentiate into urothelial cells and smooth muscle cells, but also inhibit scar formation by secreted

anti-inflammatory factors such as interleukin-10 and transforming growth factor- β, thus reducing the risk of urethral restenosis.

3.2.3 induced pluripotent stem cells

Obtained by reprogramming somatic cells, with pluripotency similar to embryonic stem cells, offers the possibility of personalized treatment of urethral strictures. However, the application of iPSCs still faces the challenges of tumorigenicity and low differentiation efficiency. A study has shown that by optimizing culturing conditions and utilizing gene editing techniques, the differentiation efficiency and safety of induced pluripotent stem cells can be significantly enhanced [20].

3.3 Regulation of Bioactive Factors

Bioactive factors (such as growth factors and gene editing techniques) play an important role in the treatment of tissue-engineering urethral stricture, which can specifically regulate cell behavior and promote tissue regeneration and functional recovery.

3.3.1 Promotion of angiogenesis

Vascular endothelial growth factor (VEGF) is a strong pro-angiogenic factor. Studies have shown that a collagen-bound VEGF-replacement scaffold in animal models showed better epithelialization, significant revascularization, and better smooth muscle regeneration than an unbound scaffold [21]. In this study, Zhu, W, et al [22] Vascular endothelial growth factor was loaded into the acellular matrix, and its ability to promote angiogenesis was verified by animal models. The results showed that the vascular endothelial growth factor-modified acellular matrix significantly increased the density and distribution of neovascularization, thereby improving the blood supply and tissue regeneration effect of the graft.

3.3.2 Inhibiting fibrosis

Transforming growth factor- β is a key regulator in fibrosis processes. Knockdown of the transforming growth factor- β signaling pathway by using transforming growth factor- β inhibitors or gene editing techniques significantly reduces scar tissue formation and reduces the rate of urethral restenosis [23].

Through the optimization of the scaffold materials, the selection and expansion of the seed cells, and the regulation of the bioactive factors. With the continuous progress of technology, more efficient and safer urethral repair therapy is expected in the future.

4. Challenges and Future Directions

Despite the remarkable progress in the clinical application of tissue-engineered urethral repair techniques, some technical bottlenecks and challenges remain, and their resolution will directly affect the further development and widespread application of the technology. At the same time, with the continuous emergence of new materials and new technologies, the future direction of tissue engineering urethral repair also presents a trend of diversification and interdisciplinary integration.

4.1 Technical Bottleneck

One of the main challenges is the ischemic problem in the central region of the graft. Since neovascularization takes time, the central area of the graft often causes cell necrosis and tissue regeneration failure due to insufficient blood supply. Immune rejection is also a great challenge, and heterogeneous or allogeneic materials may trigger a chronic inflammatory response leading to graft failure. Although the acellular matrix reduces immunogenicity by removing cellular components, its residual antigenic components may still trigger an immune response.

4.2 Future Trends

3D bioprinting offers new possibilities for tissue-engineered urethral repair. Through 3D printing, a customized stent can be built to accurately match the patients anatomical structure, thus improving the repair effect. Studies have shown that 3D-printed composite stents can not only accurately control the pore structure and mechanical properties, but also realize multi-cell co-printing, providing personalized solutions for complex urethral repair. We found that 3D printed collagen-PCL composite scaffolds exhibited excellent urethral regeneration in animal models [24]. Intelligent materials (such as pH-sensitive hydrogels, temperature-responsive materials) can dynamically regulate the drug release or scaffold performance according to the local microenvironment changes, so as to optimize the tissue regeneration process. For example, pH-sensitive hydrogels can release anti-inflammatory drugs in the inflammatory microenvironment and reduce scar formation. Moreover, responsive materials can also achieve a dynamic match with the tissue regeneration process by regulating the mechanical properties or degradation rates of the scaffold. Meanwhile, the future development of tissue engineering urethral repair is inseparable from the integration of multiple disciplines. Combining gene editing technology (such as CRISPR-Cas 9) can optimize the functional activity of seed cells and improve the efficiency of tissue regeneration [23]. The application of nanotechnology can achieve precise regulation of tissue regeneration through nanoparticles loading growth factors or drugs. In addition, the introduction of AI technology can optimize stent design and surgical planning to further improve the repair effect.

5. Conclusion

Tissue engineering has revolutionized the treatment of urethral strictures, moving from traditional surgery to regenerative medicine. Through the combination of biomaterials, seed cells and bioactive factors, the reconstruction of the anatomical structure and functional recovery of the urethra are realized, which significantly improves the quality of life of patients. However, it still faces challenges such as insufficient vascularization, immune rejection and long-term safety. In the future, advances in materials science, cell biology, and clinical technology will drive its breakthroughs.3D bioprinting can build personalized

stents, intelligent materials can dynamically respond to the micro-environment, and multi-disciplinary integration (such as gene editing, nanotechnology and artificial intelligence) provides new tools for accurate regulation and regeneration. These techniques will help tissue engineered urethral repair from the laboratory to clinically standardized therapy. In conclusion, tissue-engineering urethral repair is a new direction in the treatment of urethral stricture. Although there are technical bottlenecks, its potential has been preliminarily verified, and it is expected to become a standardized treatment plan for complex urethral stricture and benefit more patients.

References

[1] Luo H, Lou K C, Xie L Y, et al. Pharmacotherapy of urethral stricture[J]. Asian Journal of Andrology, 2024, 26(1): 1-9.

[2] Abbasi B, Shaw N M, Lui J L, et al. Posterior urethral stenosis: a comparative review of the guidelines[J]. World Journal of Urology, 2022, 40(11): 2591-2600.

[3] Tritschler S, Roosen A, Füllhase C, et al. Urethral stricture: etiology, investigation and treatments. Dtsch Arztebl Int. 2013; 110:220–6.

[4] Sun H, Zhao Z, Meng L, et al. Research advancement of tissue engineering in urology[J]. Chinese Journal of Tissue Engineering Research, 2017, 21(8): 1306.

[5] Atala A, Koh C. Applications of tissue engineering in the genitourinary tract[J]. Expert review of medical devices, 2005, 2(1): 119-126.

[6] Naud E, Rourke K. Recent trends and advances in anterior urethroplasty[J]. Urologic Clinics, 2022, 49(3): 371-382.

[7] Barbagli G, Lazzeri M. Surgical treatment of anterior urethral stricture diseases: brief overview[J]. International braz j urol, 2007, 33: 461-469.

[8] Luo H, Lou K C, Xie L Y, et al. Pharmacotherapy of urethral stricture[J]. Asian Journal of Andrology, 2024, 26(1): 1-9.

[9] Raheem OA, Buckley JC. Adjunctive maneuvers to treat urethral stricture: a review of the world literature. Transl Androl Urol. 2014;3(2):170-178.

[10] Lumen N, Campos-Juanatey F, Greenwell T, et al. European Association of Urology Guidelines on Urethral Stricture Disease (Part 1): Management of Male Urethral Stricture Disease. Eur Urol. 2021; 80(2): 190-200.

[11] Akpayak IC, Shuaibu SI, Ofoha CG, et al. Dorsal onlay buccal mucosa graft urethroplasty for bulbar urethral stricture: a single centre experience. Pan Afr Med J 2020;36:305.

[12] Horiguchi A. Substitution urethroplasty using oral mucosa graft for male anterior urethral stricture disease: Current topics and reviews. Int J Urol 2017; 24(7):493–503.

[13] Sinha R J, Singh V, Sankhwar S N, et al. Donor site morbidity in oral mucosa graft urethroplasty: implications of tobacco consumption[J]. BMC urology. 2009, 9: 1-7.

[14] Thomas W. Gilbert, Tiffany L. Sellaro, Stephen F. Badylak, et al. Decellularization of tissues and organs[J]. Biomaterials, 2006, 27(19):3675-3683.

[15] Chen, F., Yoo, J. J., et al. Acellular collagen matrix as a possible "off the shelf" biomaterial for urethral repair. Urology, 2010, 54(3), 407-410.

[16] Badylak, S. F. The extracellular matrix as a scaffold for tissue reconstruction. Seminars in Cell & Developmental Biology, 2002, 13(5), 377-383.

[17] Rashidi H, Yang J, Shakesheff K M. Surface engineering of synthetic polymer materials for tissue engineering and regenerative medicine applications[J]. Biomaterials science, 2014, 2(10): 1318-1331.

[18] Wei L, Chang H, Wang Y, et al. A gelatin/ collagen/ polycaprolactone scaffold for skin regeneration. PeerJ 7:e6358.

[19] Atala, A., Bauer, S. B., et al. Tissue-engineered autologous bladders for patients needing cystoplasty. The Lancet, 2006, 367(9518), 1241-1246.

[20] Yu, J., Hu, K., Smuga-Otto, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science, 318(5858), 1917-1920.

[21] Jia W, Tang H, Wu J, et al. Urethral tissue regeneration using collagen scaffold modified with collagen binding VEGF in a beagle model[J]. Biomaterials, 2015, 69: 45-55.

[22] Zhu, W., Masood, F., O'Brien, J., et al. Highly aligned nanocomposite scaffolds by electrospinning and electrospraying for neural tissue regeneration. Nanomedicine: Nanotechnology, Biology, and Medicine. 2016;12(3), 693-704.

[23] Bhattacharjee G, Gohil N, Khambhati K, et al. Current approaches in CRISPR-Cas9 mediated gene editing for biomedical and therapeutic applications[J]. Journal of Controlled Release, 2022, 343: 703-723.

[24] Booth D, Afshari R, Ghovvati M, et al. Advances in 3D bioprinting for urethral tissue reconstruction. Trends Biotechnol. 2024;42(5):544-559.