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Stem Cells in Urethral Replacement

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Abstract

Reconstruction of the male urethra has been and remains a challenge in adult and pediatric urology, especially for long urethral defects in the former and re-do surgery for hypospadias repair in the latter. The ability of stem cells for multipotent differentiation and the recognition of urine derived stem cells (USCs) have significantly improved the application of stem cell technology in urology, particularly for the reconstruction of urethra. USCs are recoverable from voided urine and the techniques for their recovery have improved in recent years. Stem cells from the bladder have been successfully seeded on to scaffolds for the regeneration of tubular urethra like structure.

Despite these encouraging results, many issues remain in the clinical application of stem cells in urethral regeneration and other urological procedures. These include better understanding of the multiplication potential and direction of differentiation of stem cells, functionality of the tissues generated and avoidance of harmful effects like development of neoplasms. Appropriate choice of the source of stem cells and methods of administration for the different conditions requiring their use need more research. Governing regulations in the use of stem cell therapy is another challenge that requires to be addressed.

Keywords: Stem Cells; Urology; Urethral Regeneration; Urine Derived Stem Cells

Introduction

Urethral replacement for congenital and acquired diseases of the urethra remains an important problem in urological practice. Most corrective surgical procedures use either the (a) native urethra by approximation of the normal urethral ends after excision of the pathological area (as in benign strictures (usually <3 cm in length) or (b) in situ penile tissues like the urethral plate or prepucial flaps as in primary hypospadias repair [1,2]. Longer replacements of urethra and redo hypospadias procedures may need tissue from outside the genital area, like autologous buccal mucosa. Such techniques have the disadvantages of surgery related complications, sparse donor tissue availability, patient discomfort and possibility of pathologies in the donor sites. Using tissue engineering technology, autologous cells seeded on to biodegradable scaffolds have been shown to have good outcomes when longer urethral segments need replacement. "Off-the shelf" synthetic urethral grafts without incorporation of cells and growth factors have also shown promise in urethral replacement in animals [1-4].

In general, the stem cells for therapeutic use are grouped as embryonal cells, and somatic adult cells. Embryonic stem cells from preimplantation blastocyst can form derivatives of the three primary germ cell layers. Somatic adult stem cells are of two types: Those present in mesenchymal tissues such as adipose tissue and bone as well the hematopoietic stem cells are multipotent and can differentiate into many cell types. Adult somatic stem cells present in the bladder and epidermis are oligopotent and form urothelial & smooth muscle cells and keratinocytes respectively [1,2,4]. Induced pluripotent cells are adult somatic cells that can be converted to pluripotent stem cells by exposure to transcription factors.

Once isolated, the stem cells can expand in culture, and with suitable and appropriate experimental conditions in vitro, give rise to particular cell types by induction of lineage-

specific differentiation [1,4,5]. In clinical practice, stem cells being autologous, have the advantage of not inducing immune responses and rejection.

Tissue specific somatic stem cells are normally difficult to isolate from the tissues and organs [1,4,5]. Lately, stem cells have been isolated from the urine and are referred to as urine derived stem cells (USCs). Single clones of USCs can yield a large population of cells with capacity for differentiation to uroepithelial cells and smooth muscle cells (SMCs) [1,4]. Interestingly, USCs in suitable culture conditions such as endothelial differentiation media form autologous endothelial cells which are good sources for tissue-engineered vascular regeneration or repair of endothelial dysfunction [1,5].

USCs have been seeded on biomaterials such as small intestinal submucosa, bladder submucosa or bacterial cellulose polymer [1,4,6]. By this technique, urethra like structures with urothelial and smooth muscle layers has been obtained in vitro. USCs obtained from about a quarter liter of urine can multiply to form a cell-seeded scaffold of 0.5x2x10 cm^3 in size [4]. Stem cells from the bladder tissue seeded on to a synthetic tubular scaffold was used in five boys with urethral defects with 100% success in a median follow up of about six years. However, this high success has not been reproduced again [1].

The techniques for collection of stem cells in the urine have improved in recent years and have paved the way for use of stem cells in other urological conditions such as stress urinary incontinence, vesicoureteric reflux and erectile dysfunctions [1]. Animal experiments and preclinical studies have shown promise for their use.

The clinical use of stem cells has become fairly acceptable in bone marrow transplantation for myeloproliferative disorders and some corneal defects [1,4]. In urology, the progress has not been smooth and the earlier optimism regarding the use of stem cells in stress incontinence has not been sustained [1]. However, their use for urethral replacement in cell seeded scaffolds has shown steady progress [6].

The mechanism of multiplication and differentiation of stem cells have not been clearly understood and is a factor responsible for the relatively slow progress of stem cell application in clinical practice. Mechanisms like cell contact, paracrine signaling, neovascularization, secretion of growth factors and cytokines have been postulated in stem cell multiplication [1,4,6].

Certain issues remain to be explored further in the use of stem cells in urological conditions. These are i) the influence of local factors at the site of stem cell implantation on the direction of differentiation of stem cells, ii) the source of stem cells suited for a specific disease and iii) the optimal method of administration of the cells for any particular pathological condition [1,4]. Teratoma formation is a recognized risk when pluripotent stem cells are transplanted, and their occurrence is influenced by the host's immune status [1].

For the future, research in stem cell therapy will certainly be pursued because the ability of stem cells to repair diseased tissue is definitely proven. However, the ultimate success for clinical application will depend on fully achieving the biological potential of the regenerated tissues including the neural and vascular networks of organs or tissues [1,5].

Another challenge that needs attention is the proper regulation of stem cell therapy by the regulatory authorities [1,4,5]. Very strict regulations may delay scientific progress and clinical application while lack of them would lead to false claims and potential risk to patients. The scientific community and regulatory bodies should find the correct balance between the two in their approach.

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