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Review – Reconstructive Urology

Tissue Engineering for the Lower Urinary Tract: A Review of a State of the Art Approach

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Abstract

Objectives: Tissue engineering (TE) has become synonymous with physiological and functional reconstructive approaches in medicine. Although the goals of TE are ambitious and have not yet been attained, significant milestones have been achieved and future possibilities are great. To examine these possibilities with a special emphasis on the lower urinary tract, we provide a review of the development of TE techniques and a high-level overview of related regulatory and legal issues.

Methods: Current trends in the field of TE, including the use of stem cells, scaffold optimization, and acellular tissue and growth factors, were reviewed and critically assessed through a comprehensive literature review using the PubMed database. Because of the rapid development of new TE approaches, recent abstracts from international urology conventions were included. A review of 2007 European Medicines Agency and Commission for Advanced Therapies legal regulations was also performed.

Results: Although several clinical TE approaches have been developed, most lack objective validation. A variety of TE techniques are currently under development or investigation, but thus far, no one approach is clearly superior on the basis of significant long-term studies. A medical product based on TE and stem cells can be successfully developed only with careful consideration of legal and ethical regulations.

Conclusions: TE holds the promise for a tremendous impact on reconstructive urology. However, research must be focused and intensified for the full potential clinical benefits to be made widely available. Because the product development is affected by legal regulations, consensus must be achieved.

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1. Introduction: from the enthusiastic start of tissue engineering to the mandated regulatory boundaries

During the last decade, reconstructive urology improved surgical outcomes through the use of specialized surgical equipment and the primary use of autologous or allogenic tissue. Tissue engineering (TE), with its subspecialty of stem cells, aims to treat and regenerate urological structures and organs so that full physiological function is restored [1].

The success of cell cultures depends on cell isolation, separation, and selection, as well as optimized conditions for the proliferation of single cell types [2]. In recent years, important developments such as fluorescence-activated cell sorting (FACS), immunomagnetic bead sorting, and magnetic-activated cell sorting (MACS®) enabled the selection of specific cell types [3]. Cell culturing is tailored to each individual cell type, and if stem cells are used, their differentiation to the targeted cell type is required. Biomaterials should be biocompatible, eliciting no host response, and biodegradeable within a certain time after the seeded cells have built their own extracellular scaffold to replace the biomatrix. Matrices can be artificially produced or made as an acellular scaffold from tissue. Additional growth factors support the early phase of regeneration, which might also be enhanced by genetic engineering [4–8].

Probably the most exciting and controversial area of TE is stem cells. Initially, embryonic stem cells were used due to their totipotency. However, because of their source, their use has raised moral and ethical concerns. Today, pluripotent stem cells, or differentiable adult stem cells, can be separated from many different tissues, including bone marrow [5,9,10], striated muscle [11,12], fat [13], skin [14,15], synovial membrane [16], and, more recently, testicles [17,18] and amniotic fluid [19]. They can then be differentiated into a variety of cells. In addition to resolving all these specific basic research aspects of TE, legal discussions must support the movement of TE from theory to application in clinical trials and in standard ''manufacturing'' procedures.

Thus, the optimism of the ''gold rush'' in the final years of the 20th century, when tissue-engineered artificial bladder, kidney, and penis were announced to be within a few years' reach, has subsided and given way to a more sobering and pragmatic view. This review evaluates the current state of the art in the field of TE and considers the near future, incorporates legal circumstances, and outlines realistic expectations.

2. Methods

This review is based on a search of the PubMed database of the National Center of Biotechnology Information and recently published presentations at international urology conventions for literature addressing current developments in TE and stem cells. The identified literature was critically reviewed.

The literature analysis is accompanied by a comparative discussion of the current primary trends in TE basic research followed by clinical trials, with consideration of legal and ethical issues and the integration of good medical practices (GMP) of the European Medicines Agency (EMEA) and the Committee for Advanced Therapy (CAT).

3. Results

Between January 2004 and June 2007, 347 publications addressing either TE or stem cells for the reconstruction of the urinary tract were published, one third of which were reviews (Table 1). In 2006 and 2007, respectively, there were marked increases in the number of TE and stem cell abstracts accepted for presentation at the three key urology conventions: the European Urology Association accepted 14 and 21 abstracts, the American Urology Association 9 and 32, and the DGU (Deutschen Gesellschaft für Urologie), 7 and 11.

The main goals underlying the most current TE research remains the determination of the optimum scaffold that can be seeded by cells, the best source of stem cells, and the optimal way to differentiate stem cells in urological reconstruction and regeneration. Several hundred companies are approaching the field of TE or already selling TE medical products. Research and practice needs to bear in mind the increasing regulations of the EMEA, CAT, and the United States Food and Drug Administration, depending on the confederation or country.

3.1. *Organ-specific reconstruction*

3.1.1. *Urothelium*

TE urothelium can play a key role in reconstructive urology involving urethral reconstruction (eg, repair of urethral structures, fistula, or hypospadia) and bladder reconstruction (eg, bladder exstrophy). Because no equal substitute for urothelium exists, buccal mucosa was evaluated and found to be the most adequate substitute in urethral reconstruction [20]. TE has the potential to minimize surgery time and improve the quality of repair by identifying a new source of urothelium for reconstruction through the seeding of stem cells on small intestine submucosa (SIS) (as an acellular tissue), the omentum [21], or artificial scaffolds [22,23]. Beyond these successes, a functional multilayer urothelial sheath