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European Association of Urology

Review – Reconstructive Urology

Stem Cells for Regeneration of Urological Structures

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Article info

Article history:
Accepted January 5, 2007
Published online ahead of print on January 18, 2007

Keywords:
Adult stem cells
Embryonic stem cells
Gonads
Kidney
Progenitors
Regenerative Medicine
Rhabdosphincter
Urinary tract

Abstract

Objectives: This review focuses on advances in regenerative therapies using stem cells in urology.
Methods: A detailed literature search was performed using the PubMed database of the National Center of Biotechnology Information. Publications of experimental investigations and clinical trials using stem cells in reconstructive urology have been summarized and critically reviewed.
Results: Tissue engineering and autologous cell therapy techniques have been developed to generate prostheses for different urological tissues and organ systems. During the last decade, increasing numbers of studies have described stem cells in the context of therapeutic tools. The ability of adult and embryonic stem cells as well as progenitors to improve bladder wall architecture, improve renal tubule formation, or promote restoration of spermatogenesis or recovery of continence has been investigated in several animal models. Although results have been encouraging, only a myoblast-based therapy of incontinence has reached clinical trials.
Conclusions: Several populations of adult stem cells and progenitor cells have been studied as useful cellular sources in the treatment and reconstruction of urological organs. However, considerable basic research still needs to be performed to ensure the controlled differentiation and long-term fate of stem cells following transplantion.

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1. Introduction

Tissue and organ replacement surgery often raises complications because the human immune system detects and antagonizes artificial prostheses and donor organs. The suppression of the patient's immune system often causes further unwanted side effects. Tissue replacement using autologous (stem) cell-generated material may help to overcome these problems (Fig. 1).

The genito-urinary system is exposed to a variety of possible injuries from the time of foetal development. Because most urinary organs are mainly composed of smooth muscle and uroepithelial cells,

0302-2838/$ – see back matter doi:10.1016/j.eururo.2007.01.029

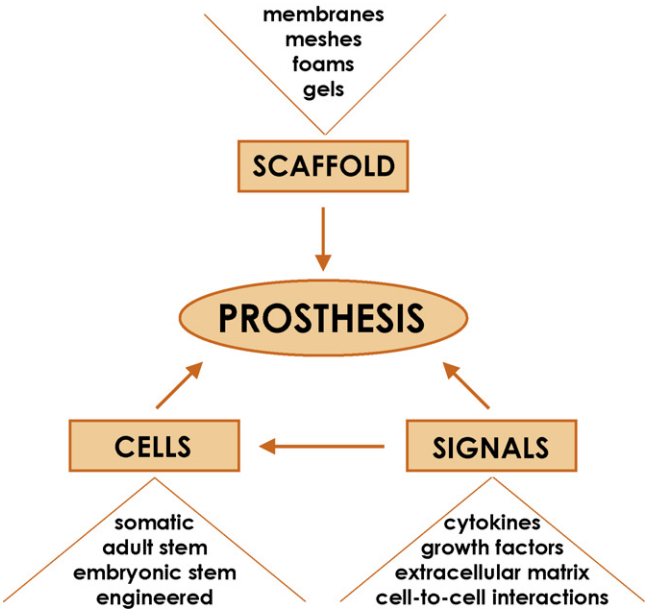

Fig. 1 – The tissue engineering triad. Tissue engineering is a multidisciplinary approach that requires material sciences to provide scaffolds and life sciences to provide living cells. To generate functional biohybrid prostheses from these substantial components, specific biologic signals provide desired phenotypes and behaviour of the cells. Increasing attention has been directed to different stem cell types.

these tissues might be repaired by autologous cell therapy techniques. In fact, in the last decade several attempts to engineer urological tissue have been reported. These include examples of biohybrid prostheses for the urethra [1], bladder [2,3], and ureter [4]. Furthermore, trials have been undertaken to reconstruct even higher complex tissues, such as renal structures [5], corpora cavernosa [6], and vaginal tissue [7]. However, only some of these approaches have advanced beyond animal experiments to human clinical studies.

Recently, Atala and coworkers reported a clinical trial of de novo tissue-engineered urinary bladders [8]. Bioartificial organs were created with autologous bladder cells seeded onto collagen-polyglycolic acid scaffolds and transplanted with an omental wrap in patients requiring cystoplasty. The engineered bladders displayed a physiologic trilayered morphology and clinical parameters such as bladder capacity, compliance, intravesical pressure, and renal function were stable at least over a 5-yr period and conformed to normal bladder values [8]. Such data have emphasized the outstanding relevance of autologous cell therapy in modern regenerative medicine. However, the use of adult organ-specific cells has several limitations, such as difficulty in harvesting, low proliferative capacity, and reduced functional quality resulting from in vitro cultivation. Furthermore, adult organ-specific cells cannot be used to treat malignant conditions. Therefore, increasing attention has been paid to pluripotent and multipotent stem cells, capable of self-renewal and tissue-specific differentiation.

2. Methods

We performed a detailed electronic literature search using the PubMed database of the National Center of Biotechnology Information. We identified relevant experimental investigations and clinical trials using stem cells in reconstructive urology for studies published before August 2006. In the process we used the following search terms: adult stem cells, autologous cell therapy, bladder, detrusor muscle, embryonic stem cells, gonads, kidney, progenitor cells, reconstructive urology, renal structures, rhabdosphincter muscle, smooth muscle cells, spermatogenesis. stem cells, tissue engineering, ureter, urethra, urinary tract, uroepithelial cells. Original peer-reviewed articles providing new substantial findings and/or presenting new experimental approaches were included to this review. For an overview of the overall state-of-the-art of science, we also included relevant review articles. Articles were summarized and critically analyzed.

3. Stem cells

Stem cells are undifferentiated cells that are defined by their abilities of self-renewal and differentiation, producing mature progeny consisting of both non-renewing progenitors and terminally differentiated effector cells [9,10].

3.1. *Stem cell populations*

It is difficult to classify stem cells due to their lack of defined morphologic and molecular characteristics [11]. Therefore, stem cells are classified according to their potency, giving rise to cells, tissues, organs, or organisms. Accordingly, the hierarchic order of stem cells ranges from totipotency to pluri- and multipotency to unipotency [12] (Fig. 2). The zygote and its offspring cells of the morula are capable of forming cells of the ectoderm, mesoderm, and (definitive) endoderm layers and the gonadal ridge, and they are also capable of forming the supporting trophoblast required for the survival of the developing embryo [13]. These cells are therefore at the top of the hierarchy of stem cells and have been termed "totipotent." Embryonic stem cells (ESCs) isolated from the inner cell mass of the blastocyst [14,15] and embryonic germ cells (EGCs) derived from

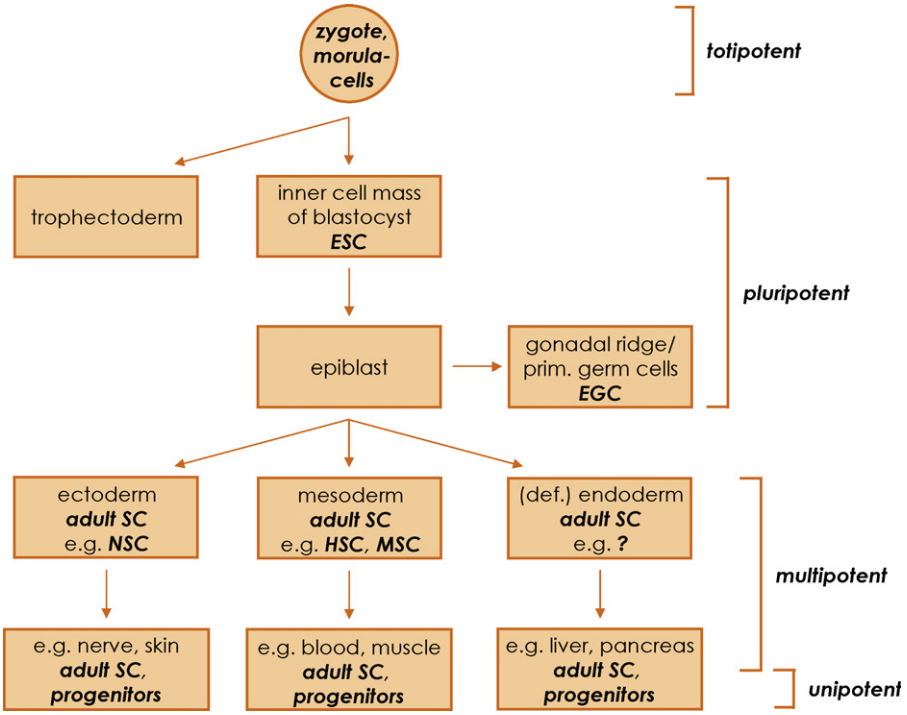

Fig. 2 – Simplified scheme of stem cell populations. Particular stem cell types are classified based on their differentiation capacity. The zygote and cells of the morula stage can give rise to both embryonic and extra-embryonic tissues and hence can generate a complete embryo. The three germ layers, as well as embryonic germ cells, originate from embryonic stem cells from the inner cell mass of the blastocyst. Adult stem cells produce progenitor cells and differentiated tissue. Figure modified after Keller [12].

primordial germ cells of an early embryo [16] can give rise to cells of the three germ layers and to those of the gonadal ridge, but not to extra-embryonic tissues. Such cells have therefore been termed "pluripotent." Stem cells isolated from the developing germ layers [17] and/or its descended adult organs [18] are capable of self-renewal and differentiate into multiple organ-specific cell types. These cells have been termed "multipotent." Examples of such multipotent adult stem cells include haematopoietic stem cells (HSC) [19], mesenchymal stem cells (MSC) [20], and neural stem cells (NSC) [21]. Progenitor cells or precursor cells that have been reported to exhibit limited or no capacity for self-renewal and differentiate into only one defined cell type, such as epithelial cells, have been termed "unipotent" [22].

3.2. *Embryonic stem and germ cells*

The derivation of murine ESC lines was described for the first time in 1981 [14] and has since proved to be a very useful tool with which to study mammalian development (which is characterized by both pluripotency and differentiation). Nearly 20 yr later, human ESC lines were successful generated [15]. ESCs can potentially be maintained in an undifferentiated state indefinitely in vitro and can theoretically be directed to differentiate into any cell type of the body. This opened visionary possibilities, such as laboratory-grown tissues or even artificial organs being created to treat a variety of diseases. Similar potencies have been described for human EGCs [16].

Both ESCs and EGCs have therefore been regarded as very interesting populations of cells for preclinical studies aimed at developing their potential for clinical applications [23]. For example, mouse ESCs have been induced to differentiate into midbrain cells (including dopaminergic neurons) by exposure to the signalling factors sonic hedgehog and FGF-8 [24]. These cells were found to be functional when transplanted into a model of Parkinson's disease. In another approach, rodent ESCs have been transplanted into the injured myocardium of infarcted hearts [25]. The phenotypes of transplanted cells ranged from striated cardiomyocytes to vascular smooth muscle cells and endothelial cells. Importantly, postinfarcted remodelling of the hearts was reduced and cardiac functions were generally improved. Although the potential of ESCs in regenerative medicine is clear, several methodological problems and issues of control of differentiation

following transplantation need to be solved before their benefit can be realized in human regenerative therapies.

3.3. *Adult stem cells*

Less controversial, but equally promising, are stem cells derived from adult human tissues, which probably have much wider differentiation potential than was previously thought [26]. According to the predestination theory, adult stem cells were thought to be developmentally committed and restricted to differentiate only into cell lineages from the tissue in which they reside, for example, NSCs give rise to nerve cells and glia, HSCs produce blood, and so on. This idea has been challenged over recent years by reports that demonstrated that adult stem cells could, under certain microenvironmental conditions, differentiate into cell types other than those of their tissue of origin. For example, HSCs have been reported to generate liver cells [27], NSCs generate haematopoeitic precursors [28], and MSCs generate neuronal cell types [29].

The biological mechanisms responsible for the broad developmental potential of stem cells derived from adult tissues are only poorly understood. Although undermined by cell fusion theories [30], a widely accepted model for this switch of cell fate that of transdifferentiation, in which certain tissues produce and suspend restrictive signals, which in turn induce the stem cells to run certain gene expression profiles and thus to undergo specific differentiation towards a certain phenotype [31]. Among the diversity of tissues reported, the bone marrow represents a major source for tissue-derived adult stem cells. This complex haematopoietic cellular system contains both HSCs and MSCs [32]. HSCs have become the most widely investigated and best understood population of adult stem cells. The transplantation of purified histocompatible HSCs can completely reconstitute the entire haematopoietic cell line in a patient after whole-body radiation or chemotherapy [33]. Increasing attention has been paid to MSCs, however, due to their versatility. MSCs have the ability to differentiate, both in vivo and in vitro, into a variety of adult mesenchymal tissue cell types (such as bone, cartilage, adipose, or muscle cells), as well as nonmesenchymal tissue cell types (such as endodermal or neural cells) [34,35]. The relatively wide range of differentiation, coupled with the high proliferation rate and relative ease of isolation of MSCs (eg, from the iliac crest), has made these cells suitable candidates for all kinds of tissue engineering and cell therapy applications. Accordingly, various case studies and clinical trials have been published that employed MSCs. These reports demonstrated MSCs in the therapeutic treatment of myocardial infarction [36], large bone defects [37], peripheral ischaemia [38], as well as in the treatment of bone-marrow suppression after high-dose chemotherapy for breast cancer [39].

4. Stem cells in urology

Research that explores the possible applications of stem cells in the field of urology has been increasing (Table 1). However, clinical transplantation studies and cell-based intervention strategies using stem cells remain limited.

4.1. *Urinary tract tissue*

Because urinary tract organs, such as bladder, ureter, and urethra, are mainly composed of two cell types, an obvious challenge would be to obtain differentiated smooth muscle and urothelial cells from stem cells or progenitors for regenerative therapies.

In vitro studies have revealed that human fat-derived MSCs can increase smooth muscle gene expression in response to dexamethasone and hydrocortisone [40]. Other researchers have emphasized that transforming growth factor (TGF) β-1 is capable of driving rat neural crest stem cells towards a smooth muscle fate [41]. Furthermore, we have investigated the potential of several stimuli to induce smooth muscle gene expression by MSCs derived from bone marrow (C. Becker, unpubl. data). In these studies, we applied different cocktails of growth factors and corticosteriods. Our results, in part, confirmed data from other groups. Moreover, we applied epithelial-mesenchymal interactions, which have been suggested to play a critical role in the development and maintenance of a smooth muscle phenotype during both embryogenesis and adulthood [42]. The combination of stimulation by humoural factors and coculture with primary urothelial cells resulted in a further significant increase of smooth-muscle-specific gene expression in the treated MSCs. However, we also demonstrated that the cells only underwent a partial differentiation (ie, when gene expression patterns of smooth muscle heavy chain or smooth muscle actin were compared with those of primary isolated smooth muscle cells from bladder). On the basis of all these data, one is drawn to the conclusion that complete smooth muscle differentiation in vitro, at present, is not possible. This difficulty is more comprehensible when considering the complexity

Table 1 – Schedule of stem-cell-related investigations and studies in the field of urology

Issue	Stem cell type	Comments	Cited reference
Differentiation of smooth muscle cells	mesenchymal stem cells derived from human fat tissue; murine neural crest stem cells	induction of smooth muscle gene expression; in vitro	Zuk et al. 2001 [40], Shah et al. 1996 [41]
Tissue engineering of bladder smooth muscle	mesenchymal stem cells derived from rat bone marrow	improvement of tissue regeneration of bladder grafts; in vivo; rat model	Chung et al. 2005 [44]
Differentiation of renal cells	murine whole bone marrow cells	induction of cortical tubular epithelial cell phenotype; in vivo; mouse model	Poulsom et al. 2001 [45]
Tissue engineering of extracorporeal bioartificial kidney	porcine renal tubule progenitor cells from embryonic tissue	improvement of synthetic haemofilter devices; in vitro/in vivo; dog model	Humes et al. 1999 [46]
Tissue engineering of intracorporeal bioartificial kidney	metanephric progenitor cells derived from bovine therapeutic cloning	generation of functional bioartificial renal units; in vivo; bovine model	Lanza et al. 2002 [47]
Tissue engineering of extracorporeal bioartificial kidney	rabbit renal progenitor cells from embryonic tissue	renal tubule formation; in vitro	Minuth et al. 2004 [48]
Recovery of spermatogenesis	murine adult spermatogonial stem cells	functional spermatogenesis; in vivo; mouse model	Brinster and Avarbock 1994 [49]
Recovery of Leydig cell function	murine adult Leydig cell progenitor cells	improvement of testosterone levels and spermatogenesis; in vivo; mouse model	Lo et al. 2004 [50]
Generation of male germ cells	murine embryonic stem cells	generation of germ cells, functional spermatogenesis; in vitro/in vivo; mouse model	Toyooka et al. 2003 [51]
Generation of male germ cells	murine embryonic stem cells	generation of germ cells, meiosis and oocyte fertilization; in vitro	Geijsen et al. 2004 [52]
Restoration of urethral sphincter muscle	progenitor cells derived from rodent skeletal muscle	improvement of sphincter muscle function; in vitro/in vivo; rat model	Cannon et al. 2003 [53]
Improvement of continence	progenitor cells derived from porcine and human skeletal muscle	improvement of rhabdosphincter muscle function; in vitro/in vivo; porcine model and human clinical trial	Strasser et al. 2004 [54]

of events leading to a smooth muscle differentiation during embryogenesis in vivo [43].

With respect to the second important cell type of urinary organs, there have been no publications describing the differentiation of stem cells towards an urothelial cell phenotype, either in vitro or in vivo.

The lack of suitable in vitro differentiation protocols for adult stem cells has led to strategies that apply ''native'' stem cells, ''predifferentiated'' stem cells, or committed precursors for transplantation. A tissue-engineering attempt using undifferentiated MSCs from rat bone marrow was performed by Chung et al. [44]. Stem cells seeded on porcine small intestinal submucosa were augmented in rats after partial cystectomy and long-term follow-up observations were made. After 3 mo, the biohybrids exhibited three-layered cellular constituents including urothelial cells and smooth muscle cells, as demonstrated by immunostaining and real-time PCR of cytokeratins 8 and 19 and smooth muscle myosin heavy chain, respectively. Although a three-layered cellular architecture was also observed in control experiments using unseeded small intestinal submucosa, only the stem-cell-seeded biohybrid exhibited gene expression levels similar to those of sham-operated animals. These results suggest that the transplanted stem cells had enhanced the sprouting of host bladder cells from the edges of the residual native tissue and probably supported the phenotypes of those cells, rather than transdifferentiated into bladder-specific cell types themselves.

4.2. *Renal tissue*

Researchers have also considered how stem cells may be used in the formation, cellular turn-over, and repair of more complex tissues, such as kidney. Poulsom and colleagues provided evidence that adult stem cells could differentiate into renal tubular epithelial cells and associated stromal cells [45]. The authors described the transplantation of whole bone marrow from male donor mice to irradiated female recipients. The presence of Y-chromosome positive staining (FISH) in recipient's kidney structures indicated a contribution by circulating bone marrow stem cells to renal epithelial cell turn-over. Moreover, integration of extrarenal circulating cells into kidney structures has also been found in humans. A series of biopsies from female kidneys that had been transplanted into male recipients has revealed the presence of Y-chromosome- and CAM5.2-positive cells, indicating the presence of cortical tubular epithelial cells derived from the male recipient. These findings underline the plasticity of adult stem cells and illustrate a new axis for kidney regeneration that suggests possible implications for renal therapy.

Accordingly, the use of renal progenitor cells to generate complex renal structures through tissue engineering approaches has been attempted. Humes and colleagues presented the concept of a bioartificial kidney composed of a standard dialysis device and a biohybrid containing renal tubule cells [46]. In an extracorporal circuit, a synthetic haemofilter cartridge was connected to a renal tubule assist device cartridge (Fig. 3). The cells incorporated into the device were derived from porcine renal tubule progenitor cells. This system successfully replaced filtration, transport, metabolic, and endocrinologic functions of the kidney in acutely uremic dogs, as assessed by plasma values and tubular fluid/ultrafiltrate ratios.

Lanza and coworkers applied the technique of somatic cell nuclear transfer, also known as therapeutic cloning, to produce histocompatible progenitor cells in a bovine model [47]. Embryonic tissue was harvested 12 wk after blastocyst transfer, and cloned metanephric progenitors were seeded onto cylindrical polycarbonate membranes. Biohybrids with collecting devices for excreted fluid were transplanted subcutaneously for 6 wk. Histological examination of retrieved implants revealed extensive vascularization and self-organization of the cells into glomeruli- and tubule-like structures (Fig. 4). The researchers noted a clear continuity between glomeruli, tubules, and the polycarbonate membrane that allowed the passage of fluid into the collecting reservoir. Importantly, secreted fluid exhibited urinelike levels for urea nitrogen/creatinine, electrolytes, and glucose, indicating that the biohybrid possessed filtration, reabsorption, and secretory capabilities.

An in vitro approach to generate a bioartificial kidney with renal progenitor cells was presented by Minuth and colleagues [48]. Renal progenitor cells from the embryonic cortex of neonatal rabbits were harvested and placed into specific tissue holders and incubated in vitro in a perfusion culture container exhibiting an artificial interstitium made of a polyester fleece. After 14 d of incubation, the generation of a wide network of numerous renal tubules at the interface of the fleece and the embryonic tissue were observed.

Although these reports sound very promising regarding a therapeutic application to patients with acute renal failure, the relatively simple configuration of the developing systems and the short incubation times are in some respects inconsistent with the complexity of nephrogenesis during

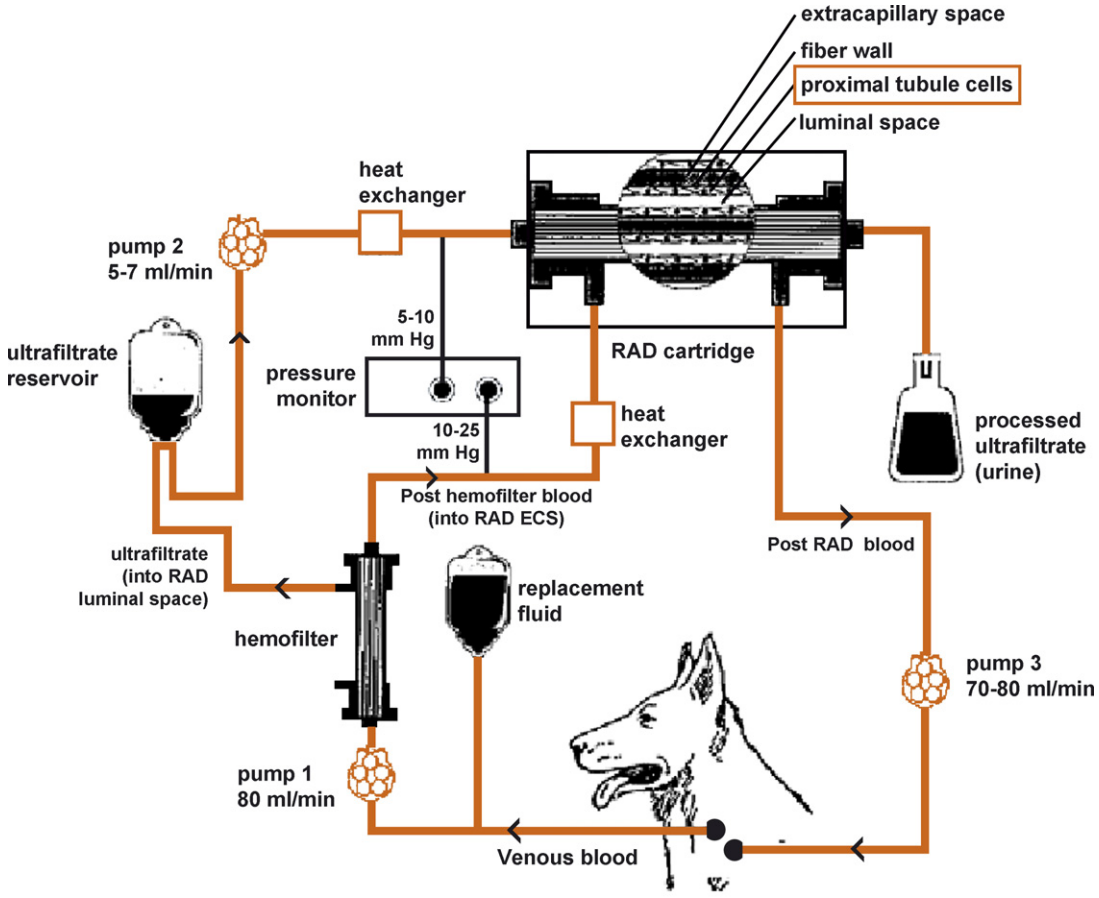

Fig. 3 – Schematic diagram of an extracorporeal haemoperfusion circuit employing a stem-cell-related bioartificial kidney [46]. A standard synthetic haemofilter cartridge is placed in series with a bioartificial renal tubule assist device cartridge, consisting of porcine renal tubule progenitor cells.

embryonic development. Ongoing investigations are required to explore further the molecular mechanisms underlying the generation of bioartificial renal devices.

4.3. *Gonadal tissue*

Brinster and colleagues described the successful transplantion of adult spermatogonial stem cells

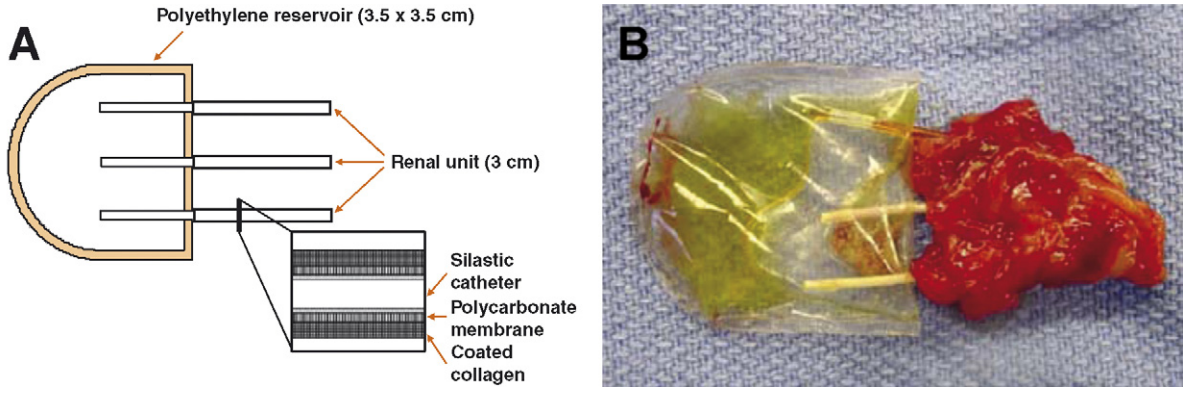

Fig. 4 – Tissue engineered renal unit [47]. (A) Illustration of biohybrid renal unit. (B) Retrieved biohybrid renal unit containing metanephric progenitor cells derived from bovine therapeutic cloning 3 mo after implantation, showing the accumulation of urinelike fluid.

into a mouse model of male infertility [49]. Donor progenitor cells from digested testicular tubules were microinjected into the seminiferous tubules of sterile recipients. After 1 mo, recovery of spermatogenesis was observed in the transplanted animals, with normal architecture of the testes. The origin of the cells responsible for functional spermatogenesis (spermatogonia, spermatocytes, and spermatids) could be assigned to the transplanted cells because these cells were derived from mice transgenic for β-galactosidase (Fig. 5, blue staining cells). Lo and colleagues embarked on a strategy in applying adult Leydig cell progenitors. Cells were isolated from adult testes of healthy mice and transplanted into the testes of LH receptor knockout recipients [50]. Such transplantations resulted in increased circulating testosterone levels and the restoration of spermatogenesis. It is possible that both of these landmark experiments could be developed for human infertility therapy, for instance, to conserve the fertility of juvenile patients undergoing radiotherapy during cancer treatment. Autologous spermatogonial stem cells could be harvested and cryopreserved prior to irradiation and subsequently retransplanted.

Other approaches to generate gametes were reported some years ago by several researchers using ESCs. For example, Toyooka and colleagues successfully isolated differentiating germ cells from embryoid body cultures derived from murine ESCs [51]. Treatment with the transcription factor bone morphogenetic factor-4 enhanced the development of the embryoid body cells towards the germ cell lines. When these cells were transplanted into the seminiferous tubules of sterile recipient mice, functional spermatogenesis could be observed. Others have demonstrated the stimulatory effect of retinoic acid on cultured murine ESCs [52]. Stimulated ESCs exhibited gene expression profiles specific to male germ cells. Cells were able to undergo meiosis and the resulting haploid gametes were able to fertilize oocytes and develop into blastocysts in vitro.

Although these investigations with ESCs are very impressive, several arguments contradict the use of ESCs in the treatment of human infertility. These include fundamental challenges and risks related to ESCs such as discussed below (see *Challenges and risks*). Furthermore, no studies have reported the successful generation of a viable embryo from ESC-derived gametes, probably due to the lack of the cells necessary for the generation of trophoblast, the cell type required for complete embryogenesis.

4.4. *Sphincter muscle tissue*

To develop suitable techniques for the treatment of urinary incontinence, two research groups have established a therapeutic strategy that depends on autologous muscle-derived progenitor cells or myoblasts and fibroblasts, respectively. Chancellor and colleagues isolated muscle-derived progenitor cells from biopsies of gastocnemius muscle of female rats by a preplate technique [53]. Animals underwent sciatic nerve lesion, resulting in almost complete loss of fast-twitch muscle contraction and partial impairment of smooth muscle contractility. Propagated progenitor cells were injected at two positions into the urethra of the incontinent animals, and restoration of deficient urethral sphincter function could be observed 2 wk after transplantation.

Strasser and colleagues advanced striated-muscle-derived myoblast transplantation from the experimental domain to human clinical trials [54]. It is noteworthy that this represents the first attempt to employ an autologous stem cell strategy in clinical urology. Cell isolation and transplantation techniques were elaborated in a porcine model (Fig. 6) and then adopted in a clinical study of 42 human urinary

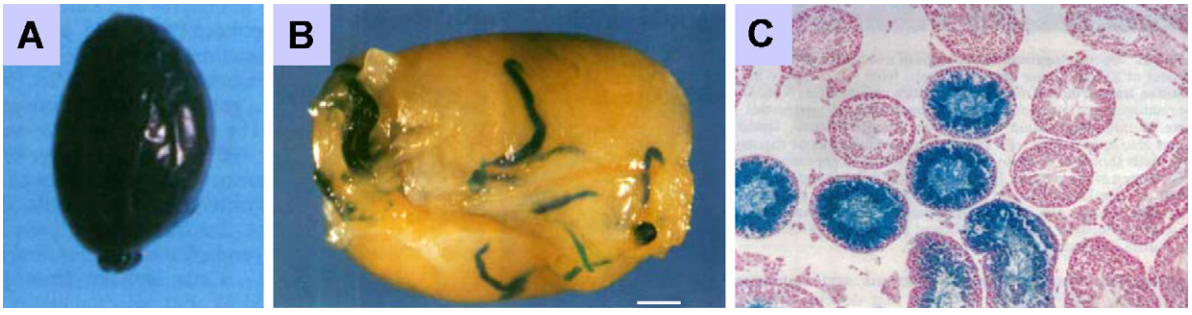

Fig. 5 – Treatment of infertility by transplantation of adult spermatogonial stem cells [49]. (A) Blue staining of donor testis with X-Gal indicates the presence of the transgene in all cells, including stem-cell areas of spermatogenesis. (B) Blue tubules indicate spermatogenesis from ZFlacZ donor spematogonial stem cells in the sterile recipient testis. (C) Blue stained tubule cross-sections represent spermatogenesis from donor stem cells.

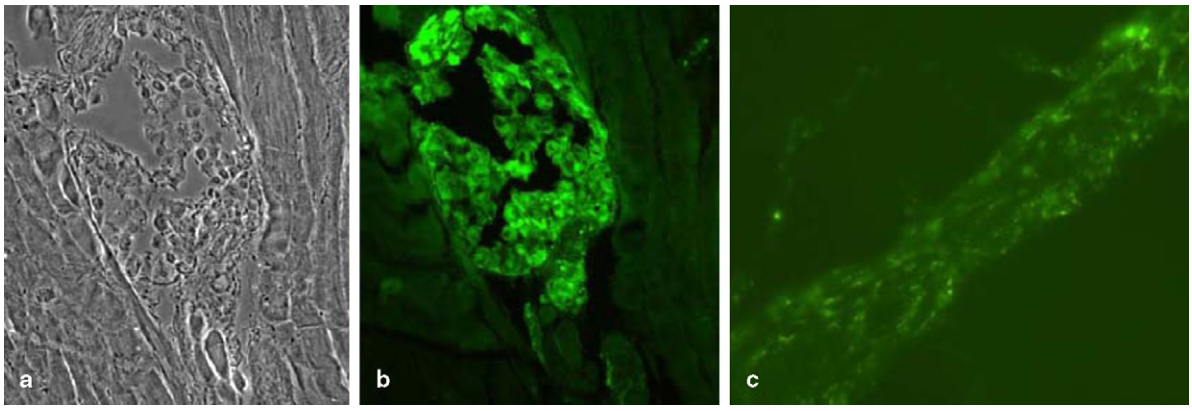

Fig. 6 – Treatment of incontinence with skeletal-muscle-derived progenitor cells [54]. Cryosections of explanted rhabdosphincters after implantation of PKH24-stained myoblasts into incontinent pigs. (a) Phase contrast microscopy of rhabdosphincter tissue 1 h after implantation. (b) Corresponding fluorescence microscopy (1 h after implantation). (c) Fluorescence microscopy of new rhabdosphincter fibres 4 wk after implantation.

stress incontinent patients [54]. Myoblasts and fibroblasts were isolated from skeletal muscle biopsies and propagated. Using transurethral ultrasound, the fibroblasts were initially injected within a collagen gel into the urethral submucosa to treat atrophies of the mucosa, followed by injections of myoblasts directly into the rhabdospincter to reconstruct the muscle. Postoperatively, patients underwent physiotherapy to train the sphincter muscle for 3 to 4 wk. The thickness of the urethrae and rhabdosphincters as well as activity and contractility of the rhabdosphincters were increased significantly. An improvement of urinary incontinence was achieved in all patients. Thirty-five percent of patients reported total continence after therapy. Because no ongoing report of this study has been published by the authors, long-term results of this therapy cannot be discussed.

Thus, available experimental and clinical data suggest that urinary incontinence can be treated by this method, supporting the notion that a therapeutic concept using autologous adult stem cells may represent a very promising modality in the future treatment of a range of disorders including urological diseases.

5. Challenges and risks

The use of stem cells to treat and reconstruct urological organs appears to be a very powerful and promising approach for the future. Due to the multitude of unanticipated problems including the handling, development, and long-term fate of stem cells, only limited applications in the field of urology have progressed beyond the experimental domain [54].

The issues of the harvesting and use of pluripotent ESCs have been extremely controversial and intensely debated in both the scientific and public arenas. Ethical and political debates have revolved around the issue since a number of human ESC (hESC) lines were made available from ''excess'' embryos from in vitro fertilization clinics. Under similar scrutiny and debate is the putative application of hESCs derived from somatic cell nuclear transfer (ie, therapeutic cloning). Nonetheless, the enormous proliferative capability and cell differentiation capacity of hESC has resulted in formulation of several methods and protocols for their potential applications in basic developmental biology and regenerative medicine. Furthermore, strategies using specific growth factor combinations and cell-cell and cell-extracellular matrix induction systems are being explored for the controlled differentiation of stem cells along a desired lineage.

The current lack of sufficient differentiation protocols is limiting the rate of progress because residual undifferentiated ESCs can pose a significant health risk of tumorigenesis following implantation into patients. In fact, there is strong evidence that hESCs transplanted into immunodeficient mice form complex teratomas consisting of a range of differentiated somatic cells, some of which appear to be highly organized, closely resembling tissues in the developing embryo and adult [55]. This exemplifies the absolute need to identify and characterize the mechanisms that control self-renewal and differentiation to improve approaches for the purification and differentiation of hESCs prior to

their application in future clinically relevant intervention strategies. Another critical issue is the morphological and developmental differences that exist between murine ESCs and hESCs, suggesting that murine models may not be adequate for direct translation to humans.

Certain adult multipotent stem cells also present several different disadvantages, principally due to the lack of unique cell surface markers, which prevents the isolation of homogenous, well-defined populations of stem cells [56,57]. Furthermore adult stem cells run the risk of senescence and epigenetic modifications, which in turn could alter the fate of the cells [56,58].

Although several methodological and bioethical obstacles need to be overcome, recent progress in experimental and clinical urology suggests that stem cells may deliver great benefits in regenerative strategies, specifically for urological structures. Further experiments and trials are therefore warranted. However, there is still much unknown territory in the field of urology, particularly regarding the introduction of stem-cell-based therapies. For example, no reports have been published using stem cells in andrology. In this context, stem cells might prove to be beneficial in the treatment of penile deformations or erectile dysfunction. Another, as-yet-unmet challenge is the development of a stem-cell-based strategy for the treatment of vesico ureteral reflux. Because the transurethral injection of autologous chondrocytes has already been demonstrated as a successful therapy of vesico ureteral reflux [59], chondrogenic differentiated stem cells could be used to guide cartilage formation in the submucosal layer [60]. The list of further putative applications of stem cells in urology can readily be extended to almost any conceivable indication.

It seems clear from the current review that the development of stem-cell-based strategies for the treatment of urological diseases or disorders is in its early stages. This provides an ample opportunity for both basic scientists and clinicians to enter this area of research.

Conflicts of interest

There are no conflicts of interest.

Acknowledgements

This study was supported by a grant from the Interdisciplinary Centre of Clinical Research ''BIOMAT'' within the Faculty of Medicine at the RWTH Aachen University (TV B100). We thank Dr. Gary Brook for linguistic revision of this manuscript.

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