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Will We Ever Use Stem Cells for the Treatment of SUI? ICI-RS 2011

Howard B. Goldman¹, Karl-Dietrich Sievert^{2,*}, and Margot S Damaser^{1,3,4,*}

¹Section of Female Pelvic Medicine and Reconstructive Surgery, Glickman Urologic and Kidney Institute, Cleveland Clinic, Cleveland, OH USA

²Department of Urology, University of Tuebingen, Tuebingen, Germany

³Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH USA

⁴Advanced Platform Technology Center, Louis Stokes Cleveland VA Medical Center, Cleveland, OH USA

Abstract

Aims—To review the current state of research in the use of stem cells for stress urinary incontinence (SUI) and assess the likelihood of this becoming a relevant treatment option.

Methods—The peer-reviewed literature consisting of relevant clinical and animal studies on the topic of SUI was surveyed and reviewed.

Results—Animal studies have demonstrated the potential utility of stem cells in promoting functional recovery of the urethra after simulated childbirth injury. Research in animals suggests similar urethral recovery after injection of bone-marrow derived mesenchymal stem cell secretions as after injection of the stem cells themselves. Therefore, whether the improvements result from the injection of the stem cells themselves or from their secretion of specific proteins is unclear. Early clinical trials have demonstrated the feasibility and short-term safety of injecting muscle-derived stem cells into the urethra to treat SUI.

Conclusions—Larger and longer term clinical trials are needed. Nonetheless, efficacious stem cell based therapy for the treatment of SUI is practical, achievable and should be available as a treatment modality in the near future.

Keywords

stem cells; urinary incontinence; stress; urethra; mesenchymal stem cells

Introduction

In the last decade the use of human stem cells (SC) has been touted as a potential breakthrough in the treatment of disease. Within the field of urology utilization of stem cells is thought to offer new therapeutic options to patients with various types of urologic disorders. Lower urinary tract dysfunction, incontinence, neurogenic bladder, ureteral and bladder trauma and various renal applications have been evaluated. While these approaches hold much promise, the practical results and treatments available to patients have been slow

Corresponding Author: Howard B Goldman MD, Center for Female Pelvic Medicine and Reconstructive Surgery, Glickman Urologic and Kidney Institute, Cleveland Clinic, 9500 Euclid Ave/Q10, Cleveland, OH, 44122, USA, 216 445-5121, goldmah@ccf.org.

*These authors jointly share the responsibility for last authorship

to materialize. Other specialties as well have not seen the rapid translation of research findings into practical treatments to the degree that was initially hoped for. While there remains much work to be done, ongoing studies in urology hold promise for development of future stem cell-based treatments. This review examines the current status of stem cell-based treatments for stress urinary incontinence (SUI) and seek to determine if we will ultimately see such treatments for SUI.

Definitions

Stem cells (SC) are cells with the capacity for perpetual self renewal (by division) and differentiation into a variety of types of cells. The degree of differentiation and the ultimate cell type formed depends on the local cellular environment. This is best illustrated by the discovery that differentiated adult cells, which are usually thought of as unipotent, or capable of only duplicating their own cell type, can differentiate into a variety of cell types if placed in an inductive cellular environment. As a result, the distinction between adult differentiated cells and SC has blurred in recent years. Nonetheless, the classic definition of SC is still utilized broadly to define and distinguish SC from other types of cells.

Embryonic SC are taken from an early stage embryo and are pluripotent or totipotent and can differentiate into all adult cell types. The use of human embryonic SCs has been limited in the United States and in most European countries due to ethical concerns with the use of such cells resulting in federal regulations that have at times hindered their use. There have also been concerns that these cells may have increased tumorigenicity potential. Adult (somatic) SCs are multipotent and have the capability of differentiating into and replenishing various tissue types. These SC make up a distinct minority of cells in a given tissue and are generally slow cycling, multipotent and are referred to by their tissue of origin.

Sources of Stem Cells

Adult SCs can be obtained from any vascularized tissue. Current thinking is that they constitute the pericytes on the vessels within tissues. Supporting evidence includes a correlation between frequency of SC-like cells and vascular density, as well as matching of cell surface markers on certain pericytes with those on certain SC, particularly on mesenchymal SC (MSC). Nevertheless it appears that all pericytes are not MSC and that MSC from different locations may behave differently¹. Thus, these cells are not identical in each tissue and therefore the source of therapeutic SC may impact efficacy. Adult SCs from muscle, bone marrow, adipose tissue, hair follicles, and recently urine (thought to originate from the pericytes of the glomerulus) have been utilized as therapeutic agents in preclinical animal studies or clinical trials.

Within the bone marrow there are three different types of SC - hematopoietic, endothelial and mesenchymal. Hematopoietic SC (HSC) give rise to the various cell lines within blood and can be harvested while circulating in the blood. Endothelial SC give rise to the endothelial cells which line the interior surface of blood vessels. Mesenchymal SC (MSC) are those that form mesenchymal cell types³. They make up only a small percentage of cells in the bone marrow and a bone marrow biopsy is required to obtain them. However, they are easy to isolate and culture, are multipotent, have reproducible characteristics from isolate to isolate, and have been used for many applications. In addition they do not express MHC class I cell surface markers or co-stimulatory molecules, but only MHC class II cell surface markers. They therefore should be invisible to the host's immune system. This feature implies that MSC from one person could potentially be utilized in another - a "universal cell" - and is potentially a significant advantage in the clinical applications compared to MDSC or ADSC.

Muscle derived SC (MDSC), are easy to obtain (via a muscle biopsy) and integrate well with host muscle tissue. In early studies it was difficult to produce high quality MDSC in adequate numbers as the majority of the transplanted cells were eliminated soon after transplantation². This problem has been solved with better plating techniques that allow for rapid expansion of cells that avoid early cell death. Typically, a subject undergoes a muscle biopsy; the MDSC are then isolated and plated and ultimately injected back into the subject at the site of interest. This can be a time consuming process that takes approximately six weeks and requires specialized equipment and sterile conditions.

Adipose derived SC (ADSC) can also be harvested in a relatively minimally invasive fashion via liposuction and large quantities of multipotent cells can be obtained without difficulty. While ADSC are easily obtained, they are not as facile as systemic stem cell types, such as bone marrow-derived SC (BMSC) or hematopoietic stem cells (HSC), at homing to sites of injury and may express surface proteins that are immunogenic. Because ADSC and MDSC express immunogenic surface proteins, they ought to be used autologously unless genetically manipulated.

Stem Cell Administration for SUI

Intravenous Injection of SC

Some types of SC can be administered intravenously and allowed to home to locations expressing homing cytokines. Homing refers to a phenomenon whereby SC transit through the circulatory system with access to all tissues in the body and migrate to specific sites that secrete factors or cytokines that attract these pleiotrophic SC to that site - such as an area of acute injury. Homing of innate SC is part of the same reparative process that brings immune cells and lymphocytes to areas of injury. For example, animal models of vaginal delivery have demonstrated that MSC migrate or “home” to sites of injury following gradients of chemokines, such as stromal derived factor 1 (SDF1) and (C-C motif) ligand 7 (CCL7), previously called MCP-3. A recent study demonstrated that intravenously injected MSC preferentially home to rat urethra, vagina, rectum and levator ani muscles 4 days after a simulated childbirth injury⁴. Since not all SC home in response to a cytokine gradient, MSC and HSC are the preferred types of SC for this route of administration. Care must be taken with this route of administration since some of the SC may localize to unexpected sites, cause microvascular occlusion, or have systemic side effects.

Urethral Injection of SC

A number of studies have evaluated direct injection of SC into the urethra in the hopes of repairing/regenerating damaged rhabdosphincter components[5–15]. Chermansky et al. demonstrated in an animal urethral trauma model that treatment with MDSC enabled significant tissue recovery compared to controls⁵. Rats that had MDSC injected into their traumatized urethras had significantly greater recovery of leak point pressure (LPP) than untreated rats. Similarly, Kim et al injected MSC into the urethra of rats that had undergone pudendal nerve dissection⁶. They demonstrated that four weeks after injection the LPP of those that had received the MSC recovered to control values; whereas rats treated with saline had significantly decreased LPP⁶. In addition, upon evaluating the transplant sites in the urethra of those who received the MSC, specific markers for smooth muscle cells were noted, indicating differentiation of the MSC into muscle.

Another animal study appears to indicate utility of ADSC for SUI⁷. At first glance, the paper by Lin, et al seems to show that SUI was improved with injection of ADSC. However, at closer review it appears they only measured bladder activity and voiding function and did not report on urethral function or response of the lower urinary tract to increases in abdominal pressure⁷, essential to diagnosis of SUI.

There was much excitement a few years ago when Strasser et al. published results of human studies in which autologous myoblasts were injected into the sphincter of women with SUI and compared that to women who received collagen injections⁸. Very impressive outcomes for the SC group were reported, but this paper was later retracted due to ethical violations and the results are generally not trusted. A report by investigators who looked into this matter “raise doubts as to whether a trial as described in *The Lancet* ever existed”⁹.

Carr et al. published a small study reporting the initial results of women with SUI who underwent urethral injection of MDSC¹⁰. Five of 8 subjects had symptomatic improvement with the onset of improvement 3–8 months after injection. At one year follow up three had been retreated and two ultimately had a sling. Of importance though, none of the subjects suffered any adverse effects.

Recently, Peters et al. reported findings of a study that utilized autologous muscle derived cells to treat SUI¹¹. Subjects underwent a biopsy of the lateral thigh muscle, and the cells were cultured and then injected into the urethral sphincter in different doses to elicit a dose-response relation. Subjects were followed for up to twelve months. No severe treatment-related adverse events occurred and minor complications occurred at a low rate and were self-limiting. Leakage, measured on 24-hour pad tests, as well as the number of SUI events, based on a 3-day diary, decreased resulting in an improved quality of life¹¹.

Another recent study that provides promise for this area evaluated safety, efficacy and quality of life changes of autologous MDSC used to treat incontinence in children with bladder extrophy-epispadias complex¹². Seven boys and one girl who had continued incontinence after bladder neck reconstruction had endourethral injection of MDSC. The one female had no significant improvement in continence though there was improvement in urodynamic parameters. The seven boys had significant improvement with 5 of them becoming continent. Importantly, this result persisted over four years of follow-up with no complications or outlet obstruction. This study, although with a group of specific patients who are quite different than the typical patient with SUI, provides evidence of the utility and success of urethral injection of MDSC for the treatment of SUI.

Others have added other materials or growth factors to SC to facilitate engraftment and growth. Xu, et al prepared MDSC mixed with fibrin glue and compared it to MDSC, fibrin glue, and a sham injection into the urethra in an SUI rat model¹³. LPP recovered in both the MDSC alone and MDSC with fibrin groups but the MDSC with fibrin group demonstrated an increased number of surviving MDSC, increased muscle/collagen ratio and a higher micro-vessel density, suggesting that fibrin glue may be a useful addition to the MDSC¹³. Another approach was taken by Zhao et al., who developed a system that included ADSC mixed with nerve growth factor (NGF) encapsulated in microspheres to allow for controlled NGF release¹⁴. These were injected periurethrally in a rat pudendal nerve transection injury model of SUI. They showed that NGF improved ADSC viability and resulted in greater improvement in LPP than other treatment groups¹⁴. Others have tried to create biocompatible slings using MSC, which are seeded on a resorbable scaffold¹⁵. Further study is necessary to see if there is any advantage to such a sling over currently available options.

Mechanism of Action

The discovery that SC engraftment, in organs distant to the site of interest, leads to improvement in function of the tissue of interest, despite a lack of local SC, caused some to wonder whether the actual repair is due to the stem cells themselves, regenerating damaged tissue, or due to factors secreted by the SC that initiate and promote tissue recovery¹⁶. Much work has now demonstrated that, in all likelihood, it is the paracrine factors secreted by the MSC that stimulate regeneration. Immunomodulatory, anti-apoptotic, angiogenic,

antifibrotic, chemoattractive and growth stimulating proteins are all secreted by these cells¹⁷. Different proteins are secreted in different micro-environments. For example, if there is a lot of inflammation present, anti-inflammatory proteins might be preferentially secreted; while if there is much fibrosis present, antifibrotic chemokines might predominate. Multiple studies along these lines have been performed in other areas including lung and cardiac disease.

In a similar vein, SC therapy has been utilized in an animal model of SUI to help answer the question of whether it is the SC themselves or the SC produced paracrine factors that impact disease. Dissaranan et al. used a vaginal distention rat model of SUI to test their theories¹⁸. In this model the vagina of a nulliparous rat is gently dilated with a foley balloon, which is left there for varying amounts of time. A prior study of this model has demonstrated an acute decrease in LPP as well as external urethral sphincter (EUS) electromyography (EMG) amplitude and frequency. First, Dissaranan et al. labeled MSC, which were injected intravenously and then imaged in the vagina and urethra to see if MSC homed to the target organs – the site of vaginal distention injury¹⁸. Second, functional recovery of LPP and EUS EMG was assessed after injecting MSC intravenously in this model. Finally, the MSC products alone – proteins produced by the cells – were injected into the exposed urethra and functional recovery was assessed. The findings showed: 1. MSC preferentially homed to the urethra, vagina and spleen; 2. LPP recovered after MSC IV injection but EMG did not; 3. Injecting the paracrine factors produced by the MSC alone (without any actual cells) led to a similar degree of LPP recovery and no EMG recovery - similar to the result with IV MSC injection¹⁸. This study clearly demonstrates that MSC home preferentially to the site of injury after vaginal distention, that they facilitate urethral functional recovery and perhaps of most interest, that the paracrine factors produced by the MSC appear to cause a similar recovery when injected locally. If found to have similar properties in humans, these factors could be used soon after tissue injury (vaginal delivery) to accelerate repair of the urethra and pelvic floor tissues. Whether a similar mechanism is responsible for improvements seen when MDSC or ADSC are utilized, remains to be seen.

Acute versus Chronic Paradigm

Even if it were possible to provide repair of damaged tissue after childbirth in the near future, there would still be many women who have sustained such injuries who would be beyond the window of opportunity for successful treatment with this paradigm. Thus in an attempt to tweak this paradigm and harness the regenerative capacities of MSC-secreted paracrine factors in chronic situations, researchers have looked into reestablishing homing by transferring genes that encode for the homing proteins into the previously damaged tissue. For example, Sundararaman et al. demonstrated that reestablishing stem cell homing by increasing SDF-1 (a homing protein released at the time of cardiac injury) expression via non-viral gene transfer into the periinfarct tissue, late after myocardial infarction, reestablished myocardial healing through recruitment of bone marrow-derived stem cells and led to improvements in cardiac function¹⁹.

Alternatively, those women might be ideal candidates for direct injection of MDSC in an attempt to utilize the SC themselves to help regenerate sphincteric tissue and provide continence²⁰. Thus, in the future there may be multiple stem cell based paradigms for the treatment of SUI: an acute paradigm whereby particular proteins are injected into the urethra soon after delivery to facilitate immediate urethral repair and functional recovery and a chronic paradigm in which women who have suffered injury in the past have regeneration of the sphincteric tissue facilitated by urethral injection of genes that awaken the homing potential of damaged tissues or SC that either stimulate regeneration or are transformed to muscle cells themselves and help recover adequate sphincter function.

Conclusion

A number of avenues to treat SUI utilizing SC have been evaluated. Animal models as well as early clinical trials have shown promising results. Whether repair is primarily via differentiation of SC themselves or via paracrine factors requires further investigation. In the future, some patients may have SUI prevented with immediate postpartum injection of “off-the-shelf” proteins into the urethra, while others who have already developed SUI may undergo injection of genes to reawaken the homing potential of the damaged tissue, or undergo a small muscle biopsy and return a few weeks later for injection of SC into the urethra, either to stimulate regeneration or to be transformed into muscle cells themselves. Either way, it appears that the answer to the question of “Will we ever use stem cells for the treatment of SUI?” is a resounding YES!

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