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Stress urinary incontinence animal models as a tool to study cell-based regenerative therapies targeting the urethral sphincter☆

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ABSTRACT

Urinary incontinence (UI) is a major health problem causing a significant social and economic impact affecting more than 200 million people (women and men) worldwide. Over the past few years researchers have been investigating cell therapy as a promising approach for the treatment of stress urinary incontinence (SUI) since such an approach may improve the function of a weakened sphincter. Currently, a diverse collection of SUI animal models is available. We describe the features of the different models of SUI/urethral dysfunction and the pros and cons of these animal models in regard to cell therapy applications. We also discuss different cell therapy approaches and cell types tested in preclinical animal models. Finally, we propose new research approaches and perspectives to ensure the use of cellular therapy becomes a real treatment option for SUI.

Contents

Abbreviations: ALPP, abdominal leak point pressure; ADSC, adipose-derived stem cells; AFSC, amniotic fluid stem cells; ASMA, alpha smooth muscle actin; BMSC, bone marrow-derived stem cells; CP, closure pressure; EFS, electrical field stimulation; EMG, electromyography; EUS, external urethral sphincter; hAFSC, human amniotic fluid-derived stem cells; hMDC, human muscle precursor cells; hUCB, human umbilical cord blood; LPP, leak point pressure; DFAT, mature adipocyte-derived cells, dedifferentiated from fat; MUCP, maximal urethral closure pressure; MSCs, mesenchymal stem cells; MDC, muscle-derived cells; MDSC, muscle-derived stem cells; MPC, muscle precursor cells; NGF, nerve growth factor; PLGA, polylactic-co-glycolic acid; PUL, pubourethral ligament; PNC, pudendal nerve crush; PNT, pudendal nerve transection; RP, radical prostatectomy; RUPP, retrograde urethral perfusion pressure; SKMSC, skeletal muscle stem cells; SUI, stress urinary incontinence; TURP, transurethral resection of the prostate; urethral pressure curve, (UPP); UI, urinary incontinence; VD, vaginal distension.

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1. Introduction

Urinary incontinence (UI) is a major health problem causing a significant social and economic impact affecting more than 200 million people worldwide [1]. The prevalence rises with age and therefore the magnitude of this problem is expected to substantially increase as the life expectancy and aging population continues to rise in the Western world [1,2]. Stress urinary incontinence (SUI) accounts for a large portion of the affected patients. SUI, as defined by the International Continence Society, is the involuntary leakage of urine on effort, exertion, sneezing, or coughing. It is estimated that one third of the procedures that are performed to treat SUI are performed on patients with recurrent disease. These currently performed procedures for SUI are usually based on compensatory and nonphysiological mechanisms. Since the ultimate success of long term management of any condition is based on an understanding of its pathophysiology, and because the pathophysiology of SUI is incompletely defined, it becomes imperative that scientists invest in the development of animal models to properly understand the condition and develop treatment alternatives based on pathophysiological changes.

The most common cause in the development of male SUI is iatrogenic sphincter damage due to radical prostatectomy (RP), transurethral resection of the prostate (TURP), and radiation therapy. SUI post-prostatectomy is of particular concern since data shows that anywhere from 2% to 66% of males are affected depending on the chosen group of patients and methods of measurement [3,4]. RP may cause direct injury to the urethral sphincter via transection, penetration, a combination of both, or indirect neuromuscular damage [5]. Over time diverse treatments for SUI have been used. Currently, the gold standard in treatment for moderate male SUI is the use of the male sling, or in the case of severe incontinence, implantation of an artificial sphincter. However, there are many complications associated with these procedures [2,6–12]. Although treatment for male SUI due to sphincter damage has evolved in the past 40 years, this disease will continue to be an unresolved social health problem. The development of new treatments focusing on cellular sphincter regeneration could play a very important role in the years to come [13].

Throughout the years different surgical treatment options for female SUI have also developed and current SUI treatments include pelvic floor physical therapy with or without biofeedback, medications such as duloxetine, urethral bulking agents, and slings [14–16]. Less commonly used but still acceptable is retropubic urethropexy surgery. In contemporary practice the use of suburethral slings has shown cost-effective objective results and subjective success [15]. In cases of severe incontinence such as intrinsic sphincter deficiency, artificial sphincter implantation is an appropriate treatment option [17] since other treatments such as placement of suburethral bands or injection of bulking agents have not proved effective enough for this condition [15,18–20]. Although the use of artificial sphincters is highly effective in severe incontinence cases, the overall complication rates are not negligible [21] and recurrence of SUI can occur. Given the proper scenario, a cell based regenerative therapy for such patients could be established as a novel treatment option for future urethral sphincter muscle regeneration [22,23].

The greatest risk factors for SUI in women are vaginal delivery and increased age [24–27]. The exact mechanism of injury is not well understood but is likely multifactorial. Vaginal childbirth produces mechanical and neurovascular injury to the pelvic floor and aging plays a negative role in the structure and function of the pelvic floor [24,28]. Combined with other potential risk factors such as parity, obesity and menopause, vaginal childbirth results in a decrease in the number and diameter of the periurethral striated and smooth muscle fibers [29–32]. As a result, patients often do not become symptomatic until years after the initial trauma of childbirth due to a cascade of events which continues to occur with age. Therefore development of animal models are also essential in understanding these events, and in the development of preventative interventions.

Maintaining urinary continence involves several aspects: i) a stable bladder with adequate capacity and accommodation, ii) an anatomically normal and functionally competent continence mechanism (consisting of a bladder neck, urethra, urethral sphincter [itself consisting of striated and smooth muscle layers, neuronal innervations, a vascular plexus, submucosa, and epithelium], endopelvic fascia, arcus tendineus and pelvic muscle support), as well as iii) the correct integrity of somatic and autonomic innervation of the structures involved [33,34]. The muscular structures are controlled by three sets of major nerves: 1) parasympathetic sacral nerves (pelvic nerves), 2) sympathetic thoracolumbar nerves innervating the periurethral smooth muscle, and 3) somatic sacral nerves (pudendal nerves) innervating the urethral striated muscles including the external periurethral sphincter and the pelvic floor muscles [35,36]. Assuming proper bladder function, damage to the urethral sphincter muscle or its innervation can be produced by various ways in both men and women, resulting in urethral sphincter damage or deficit and ultimately SUI. Thus, the mechanism of human SUI is a complex and usually multifactorial process sometimes combining denervation, muscle degeneration and apoptosis, chronic muscle atrophy, fibrosis and connective tissue disorders, among others; which makes the generation of an *in vivo* model that integrates all pathophysiological aspects conditions of SUI difficult, if not impossible.

Nevertheless, in the last 45 years several animal models for urethral dysfunction have emerged (Table 1). These models include: vaginal distension, pudendal nerve crush, urethrolysis, periurethral cauterization, urethral sphincterotomy, pudendal nerve transection, and toxins injected into the sphincter [37–41]. Some of these models were based on pathophysiological theories of urethral sphincter dysfunction, for example, the vaginal distention model was developed to *simulate maternal childbirth trauma* and its related direct sheering, ischemic or neurogenic effects on the function of the urethral sphincter. The pudendal nerve crush model is a more specific model of *neurogenic* urethral dysfunction and isolates the injuries to the pudendal nerve. Both models are unique for the characteristic of reversibility where the dysfunction in the urethral function spontaneously resolves. This characteristic is ideal for researchers who are primarily interested in understanding mechanisms of injury and repair in the pathophysiology of urethral dysfunction. Researchers interested in generating a *durable model* (defined here as SUI lasting 3 months or longer) of dysfunction have developed non-pathophysiologic based models such as urethrolysis, cauterization, and pudendal nerve transection. Therefore what is advantageous to one group may be disadvantageous to the the other group. The necessity of animal models is integral in determining the best cell therapeutic approach to treatment of SUI. However, animal models are limited in that we do not have their cooperation (for instance they cannot tell us if they