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REVIEW

Potential application of adipose tissue-derived stem cells for urological disease

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ABSTRACT

Adipose tissue-derived stem cells (ADSCs) are a somatic stem cell population contained in fat tissue that may be utilized in the treatment of urologic disease. ADSCs are excellent candidates for these therapies as they are easily obtained in large quantities from adipose tissue, and possess the potential to undergo long-term proliferation, self-renewal and multipotent differentiation. We reviewed the available evidence from 1964 through 2014 concerning ADSC availability, differentiation, and potentiality in the context of treatment for urologic diseases.

Keywords: urological disease, stem cells, adipose tissue-derived stem cell, differentiation, bladder

Adipose tissue-derived stem cells (ADSCs) [1] are a somatic stem cell population contained in fat tissue and have been shown to possess stem cell properties such as trans-differentiation and self-renewal [2,3]. Similar to other types of mesenchymal stem cells (MSCs), ADSCs express multiple CD marker antigens (CD73+CD90+CD105+ CD34+/- CD11b- CD104b- CD19- CD31- CD45- SMA- [4-7]). Additionally, utilizing ADSCs, instead of other stem cell populations, is advantageous in that large quantities of stem cells are easily isolated using minimally invasive surgical procedures.

Characterization of ADSCs

By employing flow cytometry [8], histology [9] and other methods [10,11], several candidate cellular markers and genes for ADSCs have been screened. Yamamoto et al [12] used immunofluorescence (IF) staining of mouse adipose tissue to identify cells expressing CD90, CD105, Sca-1, and/or p75NTR. The results showed widespread distribution of each of these markers, suggesting that they are not specific for ADSCs. In another recent study by Zannettino et al [13], the authors attempted to identify ADSCs in human adipose tissue by employing IF staining for cellular markers 1A6.12, 1B5, STRO-1, CD146, and 3G5. While these markers were detected in two large blood vessels of unknown identity, their location in adipose tissue cannot be inferred due to the lack of adipocytes or any other markers in the neighborhood of these two blood vessels. Several lines of evidence suggest that ADSCs are vascular precursor cells. Many studies have shown that stromal vascular fraction (SVF) contains progenitor cells that are able to differentiate into endothelial cells and participate in blood vessel formation. Additionally, a recent study demonstrated that SVF cells expressing both pericyte and mesenchymal markers reside in a periendothelial location and stabilize endothelial networks [14]. Another study showed that ADSCs transplanted into an ischemic cortex preferentially migrate toward microvessels where they differentiate into vascular smooth muscle cells [15]. Extensive histologic and flow cytometry assays, found that smooth muscle actin (SMA) and CD31 were localized within smooth muscle and endothelial cells, respectively, in all blood vessels examined. CD34 localized to both the intima (endothelium) and adventitia, neither of which expressed SMA. The niche marker Wnt5a was confined exclusively to the vascular wall, within mural smooth muscle cells. Surprisingly, the widely accepted mesenchymal stem cell marker STRO-1 was expressed exclusively in the endothelium of capillaries and arterioles but not in the endothelium of arteries. The embryonic stem cell marker SSEA1 localized to a pericytic location in capillaries and in certain smooth muscle cells of arterioles. Cells expressing the embryonic stem cell markers telomerase and OCT4 were rare and observed only in capillaries. Tang et al also identified the progenitor cells in white adipose tissue within the adipose vasculature [11]. Notably, Rodeheffer et al. reported a similar result by employing a variety of approaches [10]. Based on these findings and evidence gathered from the existing literature, it has been proposed that ADSCs are vascular precursor (stem) cells at various stages of differentiation [9].

Isolation, differentiation and application of ADSCs

In recent years, the potential for ADSCs as a new source of adult stem cells has been extensively explored [16-18]. ADSCs can be developed with a series of steps including isolation, sorting, culture and differentiation. Isolation of ADSCs begins by digesting adipose tissue with collagenase type IA. After being filtered by a cell strainer, the resulting cells are sorted by specific stem cell markers in a cytometer [1]. The sorted cells are then cultured in regular culture medium and can be induced into different cell types using an appropriate induction medium. In most animal experiments, ADSCs were isolated from autologous adipose tissue, allogeneic adipose tissue, or even heterogeneous tissue. ADSCs display multipotency by retaining the ability to differentiate into cell types of different lineages including neural tissue, smooth muscle

and endothelium. This multipotency is advantageous in the treatment of urologic diseases as all of these cell line components are important constituents of the urinary system [19].

Various routes for delivery of ADSCs, ADSC-induced cells, or ADSCs combined with compound materials have been developed for the treatment of different diseases or damaged tissue. These routes can be classified into two categories: systemic delivery through blood vessels (intravenous injection or intra-arterial injection) or local delivery directly into injured tissues or organs [20]. Although systemic injection of ADSCs has proven to be effective in some disease models, it may induce serious side effects such as respiratory distress, air embolism, or hemodynamic compromise that hinder its adoption as a regular route for ADSCs delivery [21].

ADSCs could be incorporated into damaged tissues or organs which could give rise to new functional components and also exert potent anti-inflammatory, anti-fibrotic, or immunomodulation effects through paracrine or autocrine routes (via vascular endothelial growth factor, granulocyte/macrophage colony stimulating factor, stromal-derived factor-1alpha and hepatocyte growth factor) [22,23]. Interestingly, it is proposed that even apoptotic or dying ADSCs exhibit distinctive immunosuppressive properties [24]. ADSCs have been shown to possess stronger anti-inflammatory and immuno-modulating functions than bone marrow derived MSCs [25].

The applications of ADSCs in urological disease are summarized in **Table 1**.

Application of ADSCs for kidney disease

The beneficial effects from ADSCs or MSCs have been intensively investigated for treating chronic kidney disease (CKD) or acute renal injury (AKI) [26-30]. As kidney diseases, especially CKD, usually affect multiple systems, there is a concern that autologous ADSCs may be affected by renal disease. However, results from Roemeling-van Rhijn et al. [31] have illustrated that ADSCs from patients with renal disease possessed similar characteristics and functionality as those from a healthy control group making ADSCs a feasible stem cell choice in kidney disease therapy. Many kidney diseases are associated with inflammation, altered immune response, and impaired renal units which might be ameliorated by ADSCs. Although the precise mechanisms underlying ADSCs' effect on kidney function remain unclear, it is hypothesized that ADSCs could be engrafted into glomerular or tubular structures, leading to the regeneration of tubular epithelium, and restoration of systemic or paracrine secretory function.

1. Acute renal injury (AKI)

Yasuda et al. focused their study on AKI [32] and found that subcapsular injection of non-expanded SVF cells ameliorates renal function injury induced by cisplatin in a rat AKI model. Work by the same group also explored the beneficial paracrine/endocrine effects of ADSCs on an AKI model induced by folic acid in a nude rat [33]. They found that hepatocyte growth factor (HGF) secreted by ADSCs is one of the key mediators that involved in the protection of renal function. However, Kim et al showed that human ADSCs exert a paracrine-protective effect on cisplatin nephrotoxicity at multiple target sites [34] .

2. Ischemic reperfusion (IR)

Ischemic reperfusion (IR) injury and transplantation tolerance are relevant issues associated with kidney transplants. In 2013, Vanikar et al. reported a clinical trial of a kidney transplant in a 29 year old male with end stage renal disease [35]. Pre-transplant co-infusion of donor ADSCs and hematopoietic stem cells in the kidney helped in achieving tolerance based on the results of the three year follow-up. In 2014, Iwai et al. also conducted an experiment to assess the impact of *ex vivo* administration of ADSCs on the function of kidney grafts [36]. Local administration of ADSCs to the target organ bypasses the side effects of intravenous injection of stem cells, and this can easily be implemented during the kidney transplant operation. Impressively, survival rate and renal function improved after local administration of ADSCs. In fact, even intrarenal arterial or intravenous administration of ADSCs exhibited anti-oxidant, anti-inflammatory, or anti-apoptotic properties in IR induced acute kidney injury in rat models [37-39]. In *in vitro* studies, Huang et al found that co-culture of ADSCs with renal epithelial cells enhanced the physiological function of the latter [40].

3. Chronic kidney disease (CKD)

Villanueva et al. explored the effect of ADSCs on CKD by a single intravenous infusion of ADSCs on a nephrectomy induced CKD model of rats [41]. ADSC treatment was associated with reduced plasma creatinine, higher levels of epitheliogenic and angiogenic proteins, and improved renal function. Work by Hyun et al. [42] illustrated the beneficial effects of ADSCs on improving renal function on a IgAN mouse model. These effects may occur between balancing of Th1 and Th2 cytokines that are modified by ADSCs. However not all work has demonstrated positive results. Quimby et al. investigated the safety and efficacy of intravenous infusion of allogeneic ADSCs for treatment of CKD in an elderly cat model [43] and found that both cryopreserved ADSCs and ADSCs cultured from cryopreserved adipose tissue were associated with little improvement in renal function parameters. Higher intravenous doses (4×10^6 cells/time, 3 times) of cryopreserved ADSCs were associated with a high incidence of side effects. This study illustrated that there might be different therapeutic properties between ADSCs and bone marrow derived stem cells. The use of allogeneic ADSCs might be one of the reasons for the poor outcome, since allogeneic cells survive a shorter time in the body compared to autologous ADSCs.

4. Diabetic nephropathy (DN) and others

Zhang et al. [44] found that repeated systemic administration of ADSCs attenuated proteinuria, glomerulus hypertrophy, and tubular interstitial injury in a DN rat model. Ebrahimi et al. [45] and Zhu et al. [46] focused on atherosclerotic renal artery stenosis (ARAS). With their swine models of renal injury, they found that ADSCs improved medullary inflammation, fibrosis, endoplasmic reticulum stress, and apoptosis during revascularization. These results combined with other similar reports [47] support the development of ADSC-based approaches for management of renovascular disease.

Effects of apoptotic ADSCs were also evaluated in sepsis-induced kidney injury model. Work by Chen et al. [48], Chang et al. [49], and Sung et al. [50] revealed that apoptotic ADSCs therapy led to better protection of renal function during sepsis induced by cecal-ligation and puncture (CLP). Cellular factors released from apoptotic ADSCs are thought to be responsible for their biological effect in this context.

Application of ADSCs for bladder disease

1. Bladder regeneration

Bladder wall regeneration is an unmet clinical need after subtotal cystectomy, and ADSCs have shown promising translational value in

the regeneration of bladder tissue. In *in vitro* tests, the ability of ADSCs to differentiate into cell types pertinent to the field of urology (such as urothelium and smooth muscle cells) was evaluated in several studies [51-53]. These differentiated cells exhibited relevant cell biomarkers (such as cytokeratin 18 and uroplakin II for urothelium and smooth muscle actin, myosin, and calponin for smooth muscle cells) [54,55], and maintained their viability when implanted *in vivo* [56,57]. In *in vivo* experiments, ADSCs or differentiated ADSCs (pre-cultured with ascorbic acid to enhance collagen deposition) were used to seed artificial materials or biocompatible scaffolds including tissue engineered prepuce scaffolds (TEPS) [58], polyglycolic acid (PGA) [54,59], or bladder acellular grafts (BAMG) [57]. Histological studies of these implanted materials and functional studies of the regenerated bladder found beneficial effects of ADSCs including in- vivo differentiation and immunomodulation abilities. ADSCs differentiated into epithelial and smooth muscle cells, which are normal components of the bladder wall, in these animal models. Inflammation and fibrosis appeared milder in the ADSCs seeded group, possibly resulting from the immunomodulation ability of ADSCs. ADSCs can also promote vascularization of the grafts [60]. The approaches conducted above led to higher incorporation of ADSCs into host tissues and resulted in better functional recovery.

2. Bladder voiding dysfunction (BVD)

Using a bladder outlet obstruction (BOO) induced BVD rat model, Tremp et al. proved that ADSC administration by injection into the bladder wall prevented pathophysiological remodeling caused by BOO [61]. This was also associated with regenerated bladder tissue and function recovery represented by improved voiding pressure, voiding volumes, increased smooth muscle ratio, and up-regulation of important contractile proteins. Local administration of ADSCs into the bladder wall was also associated with BOO induced detrusor overactivity (DO) according to the data of Song et al. [62]. ADSCs were able to mobilize primitive endogenous stem cells by up-regulating stem cell markers and genes responsible for stem cell trafficking (e.g., SDF-1/CXCR4, HGF/cMet, PDGF/PDGFR, and VEGF/VEGFR signaling pathways). ADSCs also ameliorated hyperlipidemia associated detrusor overactivity and diabetic bladder dysfunction (DBD) through bladder injections or intravenous injections in rat model systems according to our previous studies [63,64].

Application of ADSCs for urethral disease

1. Urethral regeneration

Tissue engineering of urethra using stem cells is another active area of translational research in urology. Both ADSCs and induced ADSCs along with biocompatible materials have shown to be an effective approach for *in vivo* building of urethral substitutes or repair material [65-67]. Engineered urethral tissue using ADSCs usually had better tissue maturation (differentiated ADSCs, collagenous fibers, extracellular matrix) and function.

2. Stress urinary incontinence (SUI)

ADSCs' therapeutic effects on another common urethral disease, stress urinary incontinence (SUI), have also been extensively explored. The strategy for treating SUI using ADSC therapy, other than as a bulking agent, allows for the possibility of functional periurethral tissue regeneration, adequate mucosal coaptation, and restoration of resting urethral closure pressure [68]. Work by Gautam et al. showed that local injection of ADSCs helped reconstruct a functional urethral sphincter in a cryoinjured urethra in a SUI rabbit model [69]. Two weeks after implantation, leak point pressure (LPP) of the ADSC-treated animals was significantly higher than that of controls. Implanted ADSCs were supposed to differentiate into skeletal muscle, smooth muscle, nerve, and endothelial cells according to their immunohistochemical analyses. Watanabe et al [70] and Wu et al [71] conducted similar experiments in a pelvic nerve injury-induced SUI model. According to their data, animals with ADSC treatment also showed significant myogenic differentiation or regeneration and improved LPP results. ADSCs combined with neuronal growth factor controlled release material might lead to better overall outcomes [72].

In 2010, we found that transplantation of ADSCs via urethral or intravenous injection was effective in the treatment or prevention of SUI in a vaginal balloon dilation model [73]. Activation of VEGF and ERK1/2 signaling pathway might be responsible for the paracrine effects of ADSCs in this model [74]. Fu et al. also explored the effect of myoblasts differentiated from ADSCs in a balloon dilation-induced SUI model. Local administration of these induced cells was also associated with improved bladder capacity and LPP [75]. Shi et al constructed a tissue engineering bulking agent with ADSCs and silk fibroin microspheres [76]. This bulking agent showed beneficial effects on an intrinsic sphincter deficiency model with long time efficacy on the recovery of the LPP and the lumen area. Finally, there are clinical trials using periurethral injection of ADSCs for the treatment of SUI in patients undergoing radical prostatectomy [77]. Preliminary data from these studies showed that local administration of ADSCs is a safe and feasible treatment modality for SUI.

Application of ADSCs for prostate disease

Takahara et al. assessed the effect of ADSCs on the proliferation of prostate cancer cells *in vitro* and *in vivo* [78]. They found that human ADSCs exerted an inhibitory effect on the proliferation of androgen responsive (LNCaP) and androgen nonresponsive (PC-3) cell lines. ADSCs activated both the TGF-β signaling pathway and caspase 3/7 signaling pathway, in addition to inducing apoptosis of both cell lines *in vitro*. During *in vivo* testing, local administration of ADSCs also delayed the growth of tumors derived from both LNCaP and PC-3 xenografts in immunodeficient mice.

In 2010, we tested the interaction of ADSCs and prostate cancer cells *in vitro* by transplanting PC-3 into the subcutaneous space of the right flank of athymic mice. One week later, ADSCs or phosphate buffered saline control was transplanted similarly to the left flank. Our results showed that the average size of PC-3 tumors in ADSC-treated mice were larger than in PBS-treated mice, and ADSCs were identified inside the tumors of ADSC-treated mice. A migration assay indicated the involvement of the CXCL12/CXCR4 axis in the migration of ADSCs toward PC-3 cells. Capillary density was twice as high in the tumors of ADSC-treated mice than in the tumors of PBS-treated mice. VEGF expression was similar but FGF2 expression was significantly higher in tumors of ADSC-treated mice than in the tumors of PBS-tread mice [79]. ADSCs helped tumor growth by increasing tumor vascularity, which was mediated by FGF2. This data cautions the use of ADSCs in cancer treatment and suggests the need for further safety study of ADSCs. In addition, it is difficult to predict the interaction between ADSCs and cancer cells *in vivo*, and ADSCs *per se* carry the risk of forming tumors when injected into the human body.

Application of ADSCs for penile disease

ADSCs are utilized more commonly in erectile dysfunction (ED) and Peyronie's disease (PD) related research [80,81].

1. Peyronie's disease (PD)

Tunica albuginea reconstruction and plaque control are important topics during the treatment of PD. Intratunical injection of ADSCs during the acute phase in a PD rat model helped prevent fibrosis and elastosis and maintain erectile function [82]. Gokce et al. showed that intratunical injection of ADSCs resulted in improved erectile function both as a prevention and treatment method in a rat model of PD [83]. Down-regulation of tissue inhibitors of metalloproteinase (TIMPs) and stimulation of matrix metalloproteinases (MMPs) might be the responsible mechanisms. Current therapeutics for tunica albuginea reconstruction using ADSCs includes the use of grafts (fascia lata, saphenous vein, porcine small intestinal submucosa, endothelialized self-assembled grafts) and ADSCs seeding [84,85]. The use of ADSCs was associated with less immunologic reaction and better maintenance of erectile function. Moreover, injected ADSCs could also be a source of endothelial and smooth muscle cells for tissue repair during PD progression [86].

Table 1. Applications of ADSCs in urological disease

Organ	Cell	Animal model	Functional change	Histological and molecular changes	References
Kidney	SVF, ADSC (rat, human, feline, swine)	Cisplatin/Folic acid induced AKI on rats, kidney transplant model, ischemia-reperfusion-induced acute kidney injury model, CKD model, IgA nephropathy model, STZ induced diabetic nephropathy model, Atherosclerotic renal artery stenosis model, sepsis induced kidney injury models	Improved survival rate, Improved renal function, increased blood flow, reduced serum creatinine and BUN, improved GFR, Reduction in proteinuria	Attenuated tubular damage, reduced apoptosis, inflammation, oxidative stress, improved revascularization, modulation of immune system	[32-50]
Bladder	ADSC	Bladder wall injury model, BOO, hyperlipidemia, diabetes induced bladder dysfunction model	Bladder wall with normal function, improved voiding pressure, voiding volumes	Differentiation and immunomodulation abilities of ADSC, promoted vascularization, increased smooth muscle ratio, unleashing/mobilizing primitive endogenous stem cells	[54-64]
Urethra	ADSC	Urethral injury model, SUI model, intrinsic sphincter deficiency model	Urethra substitute, resting urethral closure pressure restoration, improved LPP or bladder capacity	Differentiation and immunomodulation abilities of ADSC, Activation of VEGF and ERK1/2 signaling pathway	[65-77]
Prostate	ADSC	Prostate cancer model	Inhibitory effect on cancer cell, increasing tumor vascularity	Activation of TGF-β signaling pathway and caspase 3/7 signaling pathway, activation of CXCL12/CXCR4 axis, upregulation of FGF-2	[78-79]
Penis	SVF, ADSC	Peyronie's disease model, ED model (cavernous nerve injury, diabetes, radiation, hyperlipidemia)	Improved erectile function, tunica albuginea reconstruction	Down-regulation of tissue inhibitors of metalloproteinase (TIMPs), stimulation of matrix metalloproteinases (MMPs), Differentiation and immunomodulation abilities of ADSC, endothelial regeneration, Secretion of angiogenic factors, up-regulation of nNOS positive nerves and smooth muscle content, activation of FGF-2, CXC ligand 5 secretion, upregulation of SDF-1 and adrenomedullin	[80-105]

2. Erectile dysfunction (ED)

ADSCs related treatment for ED aims to replenish the damaged penile tissue and prevent further apoptosis and fibrosis, which is different from the previous "symptom alleviating" medical interventions. Song et al investigated the effect of intracavernous delivery of SVF on erectile function in a mouse model of cavernous nerve injury (CNI) [87] and found that SVF induced endothelial regeneration and restored erectile function. An important mechanism appeared to be secretion of angiogenic factors from SVF. Similar tests conducted by Das et al. [88] and Ryu et al. [89] in models of diabetic ED additionally found improved erectile function and recovery of pathological changes in SVF treated groups. Our previous work also illustrated the beneficial effect of immediate and delayed intracavernous injection of uncultured autologous SVF, penile injection of ADSCs or ADSC derived lysate in CNI model [90,91]. We also proved the beneficial effect of ADSCs on radiation induced ED model, hyperlipidemia induced ED model, and type 2 diabetes induced ED model [92-94]. Ying et al. also investigated the effect of ADSCs and ADSCs combined with autologous vein graft in the CNI model and found improved erectile function, up-regulation of nNOS positive nerves and smooth muscle content [95,96]. Liu et al. utilized ADSCs with a modified VEGF gene in the diabetic ED model and found that modified ADSCs seemed to enhance VEGF-stimulated endothelial function and stimulate the proliferation of smooth muscle cells [97]. One limitation is the lack of comparison between the effect of ADSCs and modified ADSCs or ADSCs combined with other approaches for the above two studies. There are also many reports about combined treatments that involved the administration of ADSCs for erectile dysfunction [98-101].

We have performed a number of experiments to determine the precise mechanism involved in ADSCs' effects, In 2009, our team focused on the fibroblast growth factor 2 (FGF2) related signaling pathway [102]. We found that ADSCs could differentiate into endothelial cells in the penis and FGF2 signaling mediated this differentiation. In 2011, we found that CXC ligand 5 (CXCL5) was secreted by ADSCs at a high level [103]. CXCL5 promoted MPG neurite growth and activated JAK/STAT in Schwann cells. CXCL5 may also contribute to ADSCs' therapeutic efficacy in ED animal models. Finally, in 2012 we additionally found that cavernous injury up-regulated SDF-1 expression in MPG which attracted injected ADSCs leading to the recovery of injured neurons [104]. Nishimatsu et al. also explored the mechanism involved in ADSCs induced restoration of erectile function and found that adrenomedullin (AM) played a major role in the restoration process [105].

PERSPECTIVES

ADSCs are regarded as a candidate for the treatment of urological diseases due to several advantages they offer: they can be easily obtained in large quantities under local anesthesia, possess the ability to undergo long-term proliferation, self-renewal and multipotent differentiation and serve as a vehicle for the release of neurotrophins to repair tissues damaged by disease or injury. ADSCs possess better efficacy in healing acute injuries probably because of their enhanced ability at migration and mobilization, in addition to the mechanisms related to these processes. For *in vivo* use, pre-differentiated ADSCs may be a better choice than primary ADSCs. Future directions for research in this field include activation and mobilization of endogenous ADSCs in chronic pathologies.

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