Endothelium-specific gene and stem cell-based therapy for erectile dysfunction

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Abstract

Erectile dysfunction (ED) commonly results from endothelial dysfunction of the systemic vasculature. Although phosphodiesterase type 5 (PDE-5) inhibitors are effective at treating most cases of ED, they must be taken routinely and are ineffective for a meaningful number of men. In recent years gene and stem cell-based therapies targeted at the penile endothelium have been gaining momentum in preclinical studies. These early studies reveal that gene and stem cell-based therapies may be both enduring and efficacious, and may eventually lead to a cure for ED. The following review will highlight our current understanding of endothelial-specific gene and stem cell-based therapies performed to date in a number of experimental animal models.

Keywords: erectile dysfunction; endothelial-specific gene; endothelial dysfunction; gene therapy

1 Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection of sufficient quality to permit satisfactory sexual intercourse [1]. In recent years, a growing number of studies have elucidated the role of the endothelium in the normal physiology of erections, as well as the pathophysiology of ED [2, 3]. Once believed to serve as only a passive barrier, the endothelium is now considered a primary mediator of vascular blood flow and muscle tone, as directed by neural, humoral, and mechanical stimuli.

As principally a disease of vascular origin, ED correlates highly in men with hypercholesterolemia, cardiovascular disease, hypertension, and diabetes mellitus [4]. Linking these conditions is the presence of endothelial dysfunction, a pathological state of the vasculature involving the loss of the endothelium’s responsiveness to vasodilator mediators or an increase in sensitivity to vasoconstrictors. Because ED generally presages concurrently with cardiovascular risk factors, and because cardiovascular disease has been clearly associated with endothelial dysfunction, it is reasonable to infer that ED may result from endothelial dysfunction of the penis vasculature [5, 6]. A number of both clinical and preclinical studies on hypercholesterolemia, hypertension, diabetes, and aging have demonstrated endothelial dysfunction to be a critical factor in the development of vasculogenic ED [7].

Endothelial dysfunction broadly refers to any pathological condition that inhibits the homeostatic activities of the endothelium, though the term generally connotes an attenuated endothelium-dependent smooth muscle relaxation resulting from diminished nitric oxide (NO) bioavailability within the vasculature. Although ED may be caused by an array of etiologies, endothelial dysfunction plays a preponderant role in a significant number of vasculogenic ED cases. Endothelial dysfunction within the penis is characterized by endothelial NO synthase (eNOS) uncoupling, abnormal eNOS expression and regulation, lack of eNOS substrate or cofactors, and increased oxidative stress with concomitant degradation of NO [8]. Responses to NO donors such as sodium nitroprusside in the presence of endothelial dysfunction demonstrates that the machinery for vasodilation often remains intact and that endothelium-specific aberrations...
are responsible for the diminished bioavailability of NO.

Despite the profound success of current pharmacotherapy for ED, there remains an appreciable contingent of men with intractable ED. The vascular damage accompanying diabetes, for instance, is often too disruptive to endothelial physiology to permit adequate erections, even with pharmacological intervention. It is therefore imperative to find novel ways to combat endothelial-dependent ED. Recently, preclinical studies with gene and stem cell therapies targeting the vascular endothelium in the penis have proven promising (Table 1). It is the intent of this review to survey these early studies and to foster interest into this burgeoning field of research.

2 Gene therapy for ED

The idea of gene therapy arose gradually in the 1960s and 1970s, with the first clinical experiment conducted in 1970 using the Shope papillomavirus to deliver arginase to two girls with arginemia [9]. Like many early attempts at gene therapy, this experiment failed but beckoned in an era of intensive preclinical and clinical evaluations of the concept, leading to the first clinical gene therapy cure in 2000 [10]. Introduction of exogenous genes may be accomplished through a number of vectors ranging from the viral (e.g. retroviruses, adenoviruses [Adv], Sinbisviruses) to the nonviral (e.g. liposomes or naked DNA, gold nanoparticles), though replication-deficient retroviruses, adenoviruses, and adeno-associated viruses (AAV) currently predominate most gene therapy studies in the literature. Primary drawbacks to gene therapy are random transgene expression and insertional mutagenesis.

Owing to its external positioning and limited blood flow that would hinder non-target infection in the systemic circulation, the penis is an amenable structure for gene therapy [11, 12]. In addition, cells within the penis, particularly vascular smooth muscle cells, appear to have a relatively low turnover rate. This may allow long-term expression of introduced genes and thus a more enduring therapeutic option to current pharmacological agents. Another potential benefit of gene therapy for ED is the directed correction of any aberrant biochemical pathway that manifests as penile vascular dysfunction. A number of deviant biochemical pathways are acknowledged to lead to ED, and as long as a therapeutic gene exists that can enhance or replace deficient functions it is theoretically possible to introduce the reparative gene [13]. Currently, gene therapy for ED has emphasized the NO/cGMP/protein kinase G (PKG) pathway, reflecting the principal role of NO bioavailability in the achievement and maintenance of erections [14, 15]. However, a diverse group of introduced genes corresponding to an array of biochemical pathways have shown promising preclinical results as well. In addition, a recent Phase I clinical study has established the safety and apparent efficacy of gene therapy for ED using the human smooth muscle Maxi-K channel [16]. Because the corporal endothelium is a key mediator of penile NO, many gene therapies have focused on repairing deficient endothelial NO production (Figure 1A).

2.1 eNOS gene therapy

Chiefly expressed within the endothelium, eNOS plays a vital role throughout the systemic vasculature in producing NO necessary for smooth muscle relaxation [17]. Several studies have considered eNOS gene therapy for various vascular pathologies with promising results [18–22]. In the penis, eNOS functions to maintain erections by supplying a prolonged release of NO to the overlying smooth muscle cells [2]. Diminished expression or abnormal post-translational modification of eNOS has been documented within the corpora cavernosa in a num-

Table 1. List of endothelium-specific gene and cell-based therapies for erectile dysfunction (ED). AAV, adeno-associated viruses; eNOS, endothelial nitric oxide synthase; EC-SOD, extracellular superoxide dismutase; MSCs, mesenchymal stem cells; VEGF, vascular endothelial growth factor.

<table>
<thead>
<tr>
<th>Model of ED</th>
<th>Virus or stem cell</th>
<th>Gene</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged rat</td>
<td>Adenovirus</td>
<td>eNOS</td>
<td>Champion et al. [20]</td>
</tr>
<tr>
<td>Diabetic rat</td>
<td>Adenovirus</td>
<td>eNOS</td>
<td>Bivalacqua et al. [23]</td>
</tr>
<tr>
<td>Priapic mice</td>
<td>Adenovirus</td>
<td>eNOS</td>
<td>Bivalacqua et al. [24]</td>
</tr>
<tr>
<td>Castrated rats</td>
<td>AAV</td>
<td>VEGF</td>
<td>Rogers et al. [38]</td>
</tr>
<tr>
<td>Hypercholesterolemic rats</td>
<td>Adenovirus</td>
<td>VEGF</td>
<td>Rya et al. [39]</td>
</tr>
<tr>
<td>Aged rats</td>
<td>Adenovirus</td>
<td>EC-SOD</td>
<td>Bivalacqua et al. [46]</td>
</tr>
<tr>
<td>Diabetic rats</td>
<td>Adenovirus</td>
<td>EC-SOD</td>
<td>Bivalacqua et al. [51]</td>
</tr>
<tr>
<td>Young rats</td>
<td>MSCs</td>
<td>eNOS-transduced</td>
<td>Bivalacqua et al. [77]</td>
</tr>
<tr>
<td>Young rats</td>
<td>MSCs</td>
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<td>Song et al. [78]</td>
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The critical role of eNOS in regulating erectile physiology has inspired a number of studies evaluating virally introduced eNOS to the corpora cavernosa. In a rat model of age-related ED, it was found that adenoviral gene transfer of eNOS was able to enhance erectile responses to cavernous nerve stimulation, acetylcholine, and a phosphodiesterase type 5 (PDE-5) inhibitor [20]. From this and other studies, adenoviral overexpression of eNOS increases eNOS mRNA and protein expression, as well as the predominant second messenger cGMP, within the aged penis [23]. Similarly, in a rat model of diabetic-associated ED, intracavernous eNOS transduction resulted in rectified erectile responses to cavernous nerve stimulation and increased corporal NO bioavailability [24]. In an analogous study, Bivalacqua et al. [25] demonstrated synergistic effects of intracavernous eNOS transduction and acute systemic administration of the PDE-5 inhibitor sildenafil on increasing erectile function and cGMP levels within diabetic rat penes. Paradoxically, eNOS knockout mice are subject to priapism, a consequence of downregulated PDE-5 expression with the resultant inability to break down even modest levels of cGMP [26, 27]. In an eNOS knockout mouse model of priapism, gene transfer of eNOS resulted in normalized PDE-5 expression and correction of priapic activity, providing an example of the utility of eNOS gene transfer technology to further study endothelial function [27].

2.2 Vascular endothelial growth factor (VEGF) gene therapy

One of the more intriguing determinants of erectile biology is the growth factor, VEGF. VEGF is a critical mediator of endothelial and smooth muscle physiology, and VEGF reduction is associated with a number of pathophysiological changes in the penis. In various models of ED, VEGF, as well as its receptor, flk-1, are down-regulated [28–30]. Given the critical role of VEGF in erectile biology, several studies have considered whether VEGF protein therapy ameliorates vasculogenic ED. In the first study of its kind, Henry et al. [31] evaluated the effects of VEGF protein delivery in an atherosclerotic rabbit model of ED and concluded that intracavernous injections of VEGF seemed to protect the penile corporal endothelium against the damaging effects of hypercholesterolemia. Corroborating this result, another study considering hypercholesterolemia-induced ED found evidence of hyperplasia and hypertrophy within the endothelium following intracavernous VEGF protein delivery, suggestive of active angiogenesis [32]. Animals not receiving intracavernous VEGF, however, displayed endothelial denudation and platelet attachment in the sinusoids. Further studies have shown a protective effect of intracavernously delivered VEGF protein in traumatic arteriogenic and diabetic models of ED [33–36].

Figure 1. Schematic overview of current preclinical gene- and stem cell-based therapies for treating erectile dysfunction (ED). (A): Intracavernous viral delivery of endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), and extracellular superoxide dismutase (EC-SOD) have delivered critical genes to the corporal endothelium, remedying underlying defects in vasorelaxant pathways and improving erectile function in a number of ED models. (B): Mesenchymal stem cells (MSCs), with or without eNOS transduction, have been isolated from bone marrow of syngeneic rats and injected intracavernously in an aged model of vasculogenic ED, resulting in improved NO bioavailability and erectile function.

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These studies and others have largely elucidated the mechanisms by which VEGF exerts its protective effects on the corporal endothelium. Owing to its mitogenic properties, VEGF induces hyperplasia and hypertrophy of endothelial cells, which may counteract the endothelial apoptosis common to some manifestations of ED [34]. VEGF may also directly induce anti-apoptotic pathways within the endothelium [35]. In addition, VEGF protects the endothelial response to acetylcholine, restores levels of sex hormone receptors, increases expression of eNOS, and directs stimulatory eNOS phosphorylation [31, 34, 36, 37].

Built upon the demonstrable evidence that VEGF protein therapy enhances erectile responses in disease models, along with a mechanistic understanding of how VEGF improves endothelial physiology, several recent studies have evaluated VEGF gene therapy for ED. The general intent of these studies was to ascertain whether introduced VEGF DNA would result in the long-term expression of VEGF, perhaps serving as a curative or near curative treatment for vasculogenic ED. In a model of venogenic ED resulting from castration, intracavernous delivery of VEGF mediated by AAV induced endothelial cell hyperplasia and hypertrophy, suggestive of active angiogenesis [38]. Furthermore, intracavernous AAV-VEGF delivery at the time of castration prevented venous leak and ED. Subsequently, it was discovered that intracavernous delivery of VEGF by Adv in a venogenic model of ED increases the phosphorylation of eNOS at Serine 1177, greatly enhancing NO production [37]. Adv-VEGF treated mice also demonstrated a recovery in erectile function. In contrast to wild-type mice, eNOS knockout mice were non-responsive to Adv-VEGF therapy, demonstrating a paramount role of eNOS in mediating the beneficial effects of VEGF. In a recent study of hypercholesterolemia-associated ED, intracavernous Adv-VEGF delivery greatly enhanced endothelial content of the corporal sinusoids. When combined with Adv-angiopoietin-1 (Adv-Ang1), Adv-VEGF markedly increased factor VIII-positive endothelial density within the penes of hypercholesterolemic rats. Additionally, the ratio of phospho-eNOS (Ser1177) to total eNOS was strikingly higher in hypercholesterolemic rats receiving Adv-VEGF or Adv-VEGF + Adv-Ang1 treatment. Underscoring the critical role of the endothelium in erectile physiology, Adv-VEGF alone and combined with Adv-Ang1 significantly increased erectile responses to electrical stimulation [39].

2.3 Extracellular superoxide dismutase (EC-SOD) gene therapy

Oxidative stress has been cogently demonstrated as a mediator of endothelial dysfunction within the systemic vasculature and of erectile dysfunction in the penis [40]. Reactive oxygen species (ROS), most notably superoxide, scavenge NO, forming the highly toxic peroxynitrite. Both superoxide and peroxynitrite serve to uncouple eNOS within the endothelium, which leads to yet further production of ROS. In addition, inducible nitric oxide synthase (iNOS), the Ca-independent NOS isoform, is expressed in endothelial cells under stressed conditions and further contributes to ROS production [41]. Endogenous enzymes, such as NADPH oxidase and xanthine oxidase, expressly produce ROS and are often elevated in diseases associated with endothelial dysfunction. Combating the pernicious effects of ROS are endogenous antioxidants and enzymes such as SOD. SOD catalyzes the dismutation of superoxide into hydrogen peroxide and water and is expressed in a number of cells including the vascular endothelium.

Several studies have considered the potential therapeutic effect of introducing SOD through gene therapy to quench ROS. Virally delivered SOD has yielded therapeutic effects in models of hypertension, hypercholesterolemia, heart failure, and aging [42–45]. Considering that the penile endothelium is a microcosm of the systemic vascular endothelium, a small number of pioneering studies have evaluated the therapeutic potential of intracavernous adenoviral gene transfer of EC-SOD, the predominant SOD isoform found in the vessel wall of the systemic vasculature. In a model of age-related ED in rats, Bivalacqua et al. [46] described increased superoxide production, diminished erectile responses to cavernous nerve stimulation and endothelium dependent agonists, elevated nitrotyrosine staining (a measure of oxidative stress), and reduced cGMP production in aged cavernous tissue. However, there was no commensurate increase in EC-SOD to combat the heightened superoxide levels. Upon administration of virally-introduced EC-SOD, EC-SOD mRNA, protein, and activity levels markedly increased. Furthermore, cGMP levels improved while nitrotyrosine staining within the endothelium declined. These molecular data were corroborated by salient improvements in erectile responses to cavernous nerve stimulation, as well as the endothelium-dependent vasodilator acetylcholine, demonstrating that EC-SOD gene therapy may alleviate ROS damage within the penile endothelium and restore erectile function.

Diabetes mellitus is an intricate disease with a constellation of pathophysiological etiologies and sequelae. As with age, strong evidence indicates that enhanced ROS, particularly superoxide, is a critical mediator of diabetes-related vascular dysfunction [47, 48]. Endothelial dysfunction as a result of diabetes in the penile vascular bed may be a result of ROS generation, thus decreasing NO bioavailability [49–51]. Bivalacqua et al. [51] attempted to discern whether EC-SOD gene therapy could moderate the levels of superoxide in the diabetic penis, as well as improve physiological measurements of
erectile function. The authors noted that in the diabetic penis, EC-SOD expression was insufficient to reduce superoxide production, and that overexpression of EC-SOD using an adenoviral vector attenuated superoxide levels, increased cGMP production, and significantly improved erectile physiology. These data suggest that reduction of superoxide anion improves erectile physiology through an endothelium-dependent manner secondary to improved corporal cGMP production.

2.4 Molecular targets indirectly affecting penile endothelium

Any agent that acts to increase penile blood flow will indirectly improve corporal endothelial physiology via phosphorylation of the eNOS enzyme and increased production of endothelial-derived NO. A number of gene therapies aimed at correcting neuronal or smooth muscle physiology therefore may improve endothelial function within the penis. Briefly, intracavernous gene delivery of ion channels (maxi-K channel), brain derived neurotrophic factor (BDNF), calcitonin gene-related peptide (CGRP), penile neuronal NOS (PnNOS), vasoactive intestinal peptide (VIP), insulin-like growth factor-1 (IGF-1), and PKG have all demonstrated promising preclinical efficacy at remedying ED and increasing blood flow to the penis [15, 52–57]. Irrespective of the mechanism, increased vascular shear stress resulting from enhanced penile blood flow may lead to phosphorylation of eNOS and improve endothelial derived NO biosynthesis. However, these conclusions are purely speculative at this time and need further investigation. In one of the earliest studies, iNOS was shown to demonstrate improvements to erectile physiology [58]. However, iNOS is not a normal component of penile erection and may lead to increased ROS [59]. Furthermore, inducible iNOS (iNOS) has been shown to cause endothelial dysfunction of the penile vascular bed [60].

3 Future of gene therapy for ED

Although the present preclinical gene therapy studies have demonstrated efficacy, there are a number of drawbacks that may limit their clinical implementation. First, the viral vectors evaluated so far run the risk of random transgene expression throughout the systemic vasculature. Because the vectors have demonstrated the capacity for transcytosis, virtually every cell within the body may be susceptible to transduction. Even within the penis, it would be beneficial to specify the transduction of a particular cell phenotype, such as endothelial cells or neurons—the vectors evaluated so far have demonstrated ecumenical transduction of diverse penile cells. Second, owing to the costs involved in producing viral vectors, it would be beneficial to find a way to limit the amount of virus required to efficaciously transduce penile cells. Limiting viral load requirements may also diminish the risks of inflammation and resultant fibrosis.

Recent advancements in targeting viral vectors to specific cell phenotypes may provide a solution to the above concerns. In contrast to a virus that can transduce an array of cell types, the specificity of these vectors can be finely adjusted so that expression occurs within a much more circumscribed set of cell types. If specificity can be fine-tuned, it may become possible to administer vectors systemically through intravenous injection. The viral vectors could then target appropriate cells without damaging non-targeted cells. Transcriptional targeting has been advocated as one such method of effecting specificity [61]. With transcriptional targeting, promoters are selected that are uniquely expressed within a particular cell type. That is, if smooth muscle cells are targeted, then viral genes could be linked to the promoter of desmin or some similar muscle-specific promoter. The more restrictive the promoter, the more specific the expression will be.

Alternatively, specificity could be realized through transductional targeting [62]. With transductional targeting, viral vectors are directed to transduce only those cell types that express certain membrane markers. Using this technique, it may be possible to preclude the undesired transduction of non-targeted cells. Several strategies have been suggested for achieving transductional targeting in vivo, including pseudotyping, adaptor systems, and genetic systems [63–65]. Concerning potential therapies for ED, it may be possible to devise a virus that specifically transduces target cells, thus lowering required viral load and the risk of random transgene expression. Such a highly specified vector would be desirable for systemic delivery. Even if delivery continued to be through intracavernous injection, a virus that was either transcriptionally or transductionally targeted may permit a more physiologically normal distribution of gene expression. Increased specificity of cell type expression may yield more natural responses to physiological stimuli, thus enabling more normal erection physiology.

The true potential of gene therapy to mitigate or even cure ED remains to be rigorously tested in a clinical setting. Nevertheless, a very promising Phase I clinical trial using plasmid-based gene delivery has shown that gene therapy to the penis may be both safe and effective in humans [16]. Combined with the flurry of preclinical studies with viral-based gene therapy for ED, pioneering studies such as this may lead to yet more efficacious treatments for ED in the future.

4 Stem cell primer

Stem cells have garnered significant attention recently.
for their suspected potential to treat currently intractable diseases. While some of the more extravagant claims are hyperbolic and excessively optimistic, there is clear validity to the notion that stem cells may lead to novel and potentially curative therapies. Resulting from age and degenerative diseases, cells may wear out, becoming dysfunctional or succumbing to apoptosis or necrosis. Indeed, the etiological basis for several prominent diseases, such as diabetes mellitus, sarcopenia of aging, heart failure, and Parkinson’s disease, is cell dysfunction or loss [66–69]. For these and numerous other maladies, pharmacotherapy may not be able to induce the regenerative capacity of the remaining tissue. Ostensibly, many conditions will benefit from a treatment strategy that either transplants donor cells or enhances the proliferative potential of tissue-resident stem cells, thus functionally restoring the damaged tissues.

Although variably defined, stem cells are generally attributed the capacity for 1) self-renewal, 2) differentiation into one or more distinct phenotypes, and 3) functional reproduction of damaged tissues [70]. Varying stem cell populations fall along a gradient of differentiation potential from those cells capable of becoming any cell within the organism (pluripotent), to those with more limited differentiation potential yet able of becoming several distinct cell types (multipotent), to those with the potential of becoming only one or a small number of cell types (progenitor) [71–73]. While embryonic stem cells within the inner cell mass are currently the only well-acknowledged pluripotent stem cells, the adult human has a number of multipotent and progenitor cell populations residing within various tissues and organs for the regular replacement of lost or failing cells [74].

5 Stem cell therapy for ED

Currently, only a very small number of studies have evaluated the prospects of using stem cells to treat ED [75–78], and cell-based therapy in general for treating ED is quite new [79]. However, the potentially curative nature of such treatments will undoubtedly encourage a spate of forthcoming studies with varying stem cell populations and strategies. Conceivably, stem cell therapies may reasonably obviate the need to understand the intricate molecular bases underlying ED. Current pharmacological agents target precise biochemical pathways within the penis that are aberrantly regulated under certain disease states. Because there are a myriad of potential mechanistic causes of ED, pharmacotherapy must be able to treat each etiology uniquely by correcting specific deviant pathways. By wholly replacing the operative responsibilities of dysfunctional cells, repairing specific molecular pathologies may not be critical. It is certainly an oversimplification to discount the benefits of elucidating the detailed molecular bases of ED, but much of the exciting potential of stem cells rests in their demonstrable capacity to either take over the function of lost or damaged cells or secrete compounds in situ that in some way normalize dysfunctional cells. Because endothelial dysfunction of the penile vasculature is a common cause of vasculogenic ED, rescuing the penile endothelium with transplanted stem or progenitor cells may functionally restore normal erectile responses in a large number of ED cases. Presently, only mesenchymal stem cells have been evaluated for their potential to treat vasculogenic ED (Figure 1B) [77].

5.1 MSCs

Residing within the bone marrow and a number of other tissue and organ reservoirs is a rare population of multipotent stem cells called MSCs, which are uniquely able to differentiate into a diverse array of cellular phenotypes [80–84]. Because of their combined virtues of robust proliferation, multipotency, and susceptibility to genetic manipulation, MSCs have been studied vigorously for their therapeutic potential. In preclinical studies, MSCs have shown the ability to home to and repair damaged tissues [85, 86], and clinical studies are currently monitoring their capacity to remedy a number of pathological conditions [87].

Given the right environment, MSCs have the established capacity to differentiate into diverse cell types and thus conceivably may be able to replace damaged or dysfunctional tissues of the penis. MSCs can express endothelial and smooth muscle phenotypes in vitro and have been used successfully to repair vascular diseases and insults in vivo, suggesting the possibility that this stem cell population may be effective in replacing or rejuvenating the dysfunctional analogous tissues within the penis [88–90].

At the present time, only two published studies are known to have evaluated the potential for using MSCs to treat vasculogenic ED [77, 78]. In the first of these studies, Bivalacqua et al. [77] investigated the potential of MSCs to differentiate into new endothelial cells and improve endothelial-derived NO bioavailability and erectile physiology. This and previous studies have documented that rat MSCs can be readily transduced with an Ad expressing eNOS and consequently express long-term high levels of eNOS protein, eNOS activity, and cGMP concentrations [91, 92]. Aged rats with demonstrable vasculogenic ED and reduced NO bioavailability were given intracavernous injections of MSCs with or without transduction with eNOS. Seven days after injection the MSCs were adhered to the endothelium, and after twenty-one days many of the cells were expressing endothelial antigens. eNOS expression/activity, cGMP, and erectile responses were significantly increased within the penis after twenty-one days in both the normal and
transduced MSCs, suggesting the long-term capacity of these cells to replace dysfunctional endothelial cells. In addition, no signs of inflammation were noted at 7 and 21 days following injection of MSCs.

Subsequently, Song et al. [78] evaluated the potential of immortalized human fetus-derived MSCs to differentiate into endothelial and smooth muscle cells within rat corpora cavernosa. The immortalized MSCs were injected into the cavernosa of young, healthy rats, and two weeks later the penes were collected and studied for endothelial and smooth muscle antigens. Histological assessment of the penes revealed the expression of endothelial-specific antigens within the corpora, suggesting that many of the MSCs had differentiated into endothelial-like cells. Considered together, these two early studies appear to provide evidence for the potential of MSCs from various sources to differentiate into fully functional endothelial cells and palliate both endothelial-dependent NO bioavailability and erectile responses.

6 Conclusion

As the primary mediator of NO-derived smooth muscle relaxation, the penile endothelium is critical for normal erectile physiology. Although PDE-5 inhibitors are highly efficacious for a majority of men with ED, a large contingent are unresponsive or have strict contraindications to the drug and require alternative treatment options. In addition, a drawback to oral pharmacotherapy is the requirement for routine administration. Preclinical gene and stem cell-based therapies demonstrate apparent long-term efficacy in animal models. Alred, gene therapy for ED is being evaluated in clinical trials, and stem cell-based approaches will likely follow. Combined with the remarkable success of PDE-5 inhibitors, endothelial-specific gene and stem cell-based therapies may someday add to our growing armamentarium against ED.

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