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Review Article

Therapeutic Angiogenesis as a Potential Future Treatment Strategy for Erectile Dysfunction

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The cavernous endothelium plays a crucial role in regulating the tone of the underlying smooth muscle and physiologic penile erection. Recently, the link between erectile dysfunction (ED) and cardiovascular disease was unveiled, and the main etiology of ED was found to be vasculogenic. Although oral phosphodiesterase-5 inhibitors are generally effective for men with ED, such therapies do not cure underlying vasculopathy in the corpus cavernosum tissue. This review addresses current preclinical protein, gene, and cell or stem cell therapies for enhancing cavernous endothelial regeneration and restoring erectile function.

Key Words: Erectile dysfunction, Endothelium, Angiogenesis inducing agents

INTRODUCTION

The vascular endothelium plays an important role in the regulation of vascular tone and blood flow.[1] The cavernous endothelium, which is located on the inner surface of the lacunar spaces in the erectile tissue, also plays a crucial role in regulating the tone of the underlying smooth muscle and physiologic penile erection.[2] Recently, a link between erectile dysfunction (ED) and cardiovascular disease was uncovered and both diseases were shown to share the same risk factors, including hypercholesterolemia, hypertension, diabetes mellitus, and smoking, with endothelial cell dysfunction being the common denominator between these two conditions.[3,4] Although oral phosphodiesterase -5 inhibitors are generally effective for men with ED,[5-7] such therapies do not cure underlying vasculopathy in the corpus cavernosum tissue. Therefore, development of a new therapeutic strategy that reestablishes the structural and functional microvasculature in the erectile tissue is needed to cure ED. This review addresses current preclinical studies targeting cavernous endothelial regeneration, including angiogenic factor protein or gene therapy, and cell or stem cell therapy to restore erectile function.

CHANGES IN EXPRESSION OF ANGIOGENIC GROWTH FACTORS IN ED

Several lines of evidence have demonstrated the down-regulation of angiogenic growth factors in the corpus cav-

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ernosum tissue of vasculogenic ED. We previously determined the differential expression of angiogenic factors and their downstream target molecules in the corpus cavernosum of the hypercholesterolemic rat, induced by a diet containing 4% cholesterol and 1% cholic acid for 3 months.[8] Analysis by reverse transcription polymerase chain reaction and western blot showed significantly lower gene expression of vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang1) and significantly lower protein expression of VEGF, Ang1, and the ratio of phospho-Akt to Akt, and phospho-endothelial nitric oxide synthase (eNOS) to eNOS in hypercholesterolemic rats than in controls. Cavernous tissue cyclic guanosine monophosphate (cGMP) concentrations and endothelial area were also significantly lower in hypercholesterolemic rats than in controls.[8] It was also reported that the expression of VEGFR-2 was decreased in the corpus cavernosum tissue of hypercholesterolemic rabbits fed a 0.5% high cholesterol diet.[9,10] The cavernous expression of VEGF increased in the early phase after initiation of a high cholesterol diet and decreased in the late phase.[9,10] The expression of VEGF was also reported to be decreased in the corpus cavernosum tissue of ageing men compared with young controls.[11] These findings give us a clear rationale for the use of angiogenic factor to treat ED from vascular risk factors.

PROTEIN OR GENE THERAPY WITH ANGIOGENIC GROWTH FACTOR

To date, many investigators have reported the results of angiogenic growth factor therapy by use of direct protein delivery or gene transfer (Table 1).[12-18] Of angiogenic growth factors, VEGF and Ang1 have been the most extensively studied. Local intracavernous delivery of the VEGF gene or protein has been shown to cause erectile function to be recovered in rat models of vasculogenic ED induced by castration,[12] diabetes,[13,15] or dyslipidemia.[14] These studies did not report whether VEGF therapy induces regeneration of cavernous endothelial cells; however, physiologic improvement, such as partial or complete recovery of erectile function, was noted. Furthermore, it was reported that VEGF administration can initiate vessel formation in adult animals, but by itself promotes the formation of only leaky, immature, and unstable vessels,[19-21] which greatly limits the therapeutic utility of VEGF. In comparison, Ang1, the ligand of the Tie-2 receptor, is known to generate non-leaky, stable, and mature blood vessels in pre- and postnatal angiogenesis.[22,23] Ang1 also counteracts VEGF-induced inflammation in endothelial cells while having an additive effect on vessel formation.[24,25] Previous studies have shown that co-administration of Ang1 and VEGF profoundly enhanced revascularization in ischemic animal models.[24-26] We demonstrated in a rat model of hypercholesterolemic ED that adenoviral-mediated combined gene delivery of Ang1 and VEGF into the corpus cavernosum produces an additive effect on erectile function through complete restoration of cavernous endothelial cell content compared with that of either therapy alone.[16] We also reported that in mouse models of type I and type II diabetic ED a single in-

Table 1. Preclinical *in vivo* angiogenic growth factor therapies for erectile dysfunction

Authors	Protein or gene	Animal model	Duration	Efficacy
Rogers et al[12]	AAV-VEGF	Castrated rats	1 mo	Partial
Dall'Era et al[13]	PEI-pEGFP-VEGF	DM rats (STZ)	3 wk	Partial
Gholami et al[14]	VEGF protein	Dyslipidemic rats	4 mo	Partial
Yamanaka et al[15]	VEGF protein	DM rats (STZ)	6 wk	Complete
Ryu et al[16]	Ad-CMV-Ang1+Ad-CMV-VEGF	Dyslipidemic rats	8 wk	Complete
Ryu et al*	Ad-CMV-COMP-Ang1	Dyslipidemic mice	8 wk	Complete
Jin et al[17]	Ad-CMV-COMP-Ang1	DM mice (STZ)	4 wk	Complete
	COMP-Ang1 protein	DM mice (STZ)	4 wk	Complete
Jin et al[18]	COMP-Ang1 protein	db/db mice	2 wk	Complete

AAV: adeno-associated virus, VEGF: vascular endothelial growth factor, PEI: polyethyleneimine, EGFP: enhanced green fluorescent protein, DM: diabetes mellitus, STZ: streptozotocin, ad: adenovirus, CMV: cytomegalovirus promoter, Ang1: angiopoietin-1, COMP: cartilage oligomeric matrix protein.
*Unpublished data.

tracavernous injection of adenovirus-mediated synthetic Ang1 gene, a soluble and potent Ang1 variant, or two successive intracavernous injections of synthetic Ang1 protein significantly increased cavernous endothelial cell proliferation, eNOS phosphorylation, and cGMP expression and decreased the production of reactive oxygen species, such as superoxide anion and peroxynitrite.[17,18] These changes restored erectile function up to 4 weeks in the diabetic mice. Interestingly, two successive administration of synthetic Ang1 protein induced similar improvement in erectile function in the diabetic mice as compared with those that received a single injection of synthetic Ang1 gene. The relatively long-term recovery of erectile function achieved with angiogenic factor protein is noteworthy because the use of therapeutic protein is safer than the use of genes to treat human ED.

GENE DELIVERY VECTORS

Gene therapy has been attempted in the field of ED arising various pathologic conditions. However, no therapeutic genes have so far been approved for the treatment of patients with ED despite promising results at the preclinical level. One important reason for this lack of approval is the infidelity of the current gene delivery methods for the treatment of ED. Viral or naked plasmid vectors have been used the most in preclinical trials of gene therapy for ED.[27] Although viral vectors have a high transfection efficiency, their utility in clinical situations is limited by the risks of immunogenicity or mutagenesis. Naked plasmid DNA (pDNA), by contrast, is safe in regard to the cytotoxicity and immunogenicity, but the low transfection efficiency is a barrier to clinical application.[28,29] Therefore, a prerequisite for the successful application of gene therapy in human diseases, especially in a non-life-threatening disease like ED, is the development of efficient gene delivery systems with a good safety profile.

A decrease in intracavernous oxygen tension, that is, cavernous hypoxia, as well as an increase in the cavernous expression of hypoxia-inducible factor-1 α, was noted in animal models of vasculogenic ED induced by traumatized iliac arteries or a high-cholesterol diet.[30,31] Therefore, development of a gene delivery system that induces gene expression in ischemic tissue but not in normal tissue, is useful for the delivery of therapeutic genes in an ischemia-specific manner. Recently, hypoxia-inducible gene expression systems, RTP801 promoter and erythropoietin (Epo) enhancer, have been introduced to enhance gene transfer into the ischemic issue and they induce gene expression in a hypoxia-dependent manner.[30,32] We have demonstrated that luciferase gene expression was significantly induced by Epo enhancer and RTP801 promoter in both the corpus cavernosum tissue of hypercholesterolemic mice *in vivo* and in primary cultured mouse cavernous endothelial cells exposed to hypoxic conditions *in vitro*.[32] In contrast, gene expression was not induced in normal corpus cavernosum tissue or in mouse cavernous endothelial cells exposed to normoxic conditions, which may prevent the undesirable expression of the exogenous gene in nonischemic areas. Interestingly, the expression of exogenous gene by Epo enhancer and RTP801 promoter was largely confined to the cavernous endothelial cells and not present in the smooth muscle cells.[32] Therefore, it seems particularly advantageous to apply the hypoxia-inducible gene expression system to genes targeting endothelial cell regeneration, such as VEGF and Ang1. The endothelial cell-specific expression of therapeutic genes will enable us to determine the exact function of the target genes.

The development of a nonviral gene delivery system by using a variety of polymer-based gene carriers is another important field of research. Cationic polymers have been developed because the interaction between positively charged particles and negatively charged cell membranes can accelerate the cellular uptake of DNA.[33] Among the cationic polymers, poly (ethyleneimine) (PEI) is one of the most efficient vectors and is known to display high transfection efficiencies in many cell lines.[34] Previous studies reported that in a rat model of diabetes VEGF gene therapy with the use of a PEI gene delivery system improved erectile function.[13] Despite the relatively high transfection efficiency of PEI, however, its use as a gene carrier in humans is greatly limited because of its high cytotoxicity, mostly as the result of nondegradability and accumulation.[35] We previously evaluated water-soluble lipopolymer (WSLP) as a polymeric gene carrier to the corpus cavernosum.[36] WSLP was synthesized by the conjugation of cholesterol to low molecular weight PEI (PEI1800, 1.8 kDa). WSLP/

pDNA complex had high transfection efficiency, which was comparable to PEI, and less cytotoxicity than PEI in the A7r5 vascular smooth muscle cell line *in vitro*, suggesting that WSLP is a safer carrier than PEI. Moreover, WSLP/pDNA complex showed higher transfection efficiency than naked pDNA and similar transfection efficiency to PEI in rat corpus cavernosum tissue.[36] We recently observed that a gene delivery system with guanidinylated bioreducible polymer (GBP) polyplexes, which utilize the advantages of the biodegradability of reducible disulfide bonds and the cell-penetrating ability of guanidine groups, had minimal cytotoxicity and displayed higher transfection efficiency than did the cytomegalovirus promoter in hypercholesterolemic corpus cavernosum tissue *in vivo* and in primary cultured mouse cavernous endothelial cells *in vitro* (unpublished observation). It would be interesting to apply GBP polyplexes with or without hypoxia-inducible gene expression systems for the delivery of angiogenic factor genes to treat vasculogenic ED.

CELL OR STEM CELL THERAPY TARGETING ENDOTHELIAL CELL REGENERATION

Recently, much attention has been given to cell or stem cell therapy for the treatment of ED at the preclinical level. Cell or stem cell therapies targeting cavernous endothelial cell regeneration in animal models for ED from vascular causes are summarized in Table 2.[37-40] Previous studies have reported that in animal models for diabetes and dyslipidema cultured adipose tissue-derived stem cells or bone marrow-derived stem cells increased cavernous endothelial cell content and restored erectile function.[37-39] Meanwhile, it has been reported that adipose tissue-derived stromal vascular fraction (AD-SVF) is an ideal source of stem cells that can be easily harvested in high quantities through minimally invasive procedures.[41,42] AD-SVF is known to promote neovascularization in the ischemic condition *in vivo* by direct differentiation into vascular endothelial cells or by paracrine effects, i.e., secreting angiogenic factors.[43,44] We recently observed in a mouse model of type I diabetes that a single intracavernous injection of freshly isolated AD-SVF significantly increased cavernous endothelial cell proliferation, eNOS phosphorylation, and cGMP expression, which resulted in the recovery of erectile function in diabetic mice.[40] Although some AD-SVF underwent differentiation into endothelial cells, the frequency of this event was relatively low. We found a significant increase in VEGF expression in the cavernous tissue of diabetic mice 1 day after intracavernous administration of AD-SVF. Moreover, AD-SVF-induced cavernous angiogenesis and subsequent restoration of erectile function was abolished or reduced in the presence of VEGF-Trap, a soluble VEGF-A neutralizing antibody,[40] which supports the paracrine effects of AD-SVF rather than the direct differentiation of AD-SVF into endothelial cells.

The use of freshly isolated AD-SVF has many advantages: this fraction can be easily harvested from ED patients in great quantities with simple and minimally invasive techniques, and AD-SVF can be reintroduced into the corpus cavernosum of ED patients without further *in vitro* selection or expansion of the cells. We believe that local delivery of freshly isolated AD-SVF will be a useful autologous treatment option for curing vascular disease-induced ED. Similar to the results of the other stem cell therapies with cultured adipose tissue-derived or bone marrow-derived stem cells, however, the effect of

Table 2. Preclinical *in vivo* cell/stem cell therapies for erectile dysfunction targeting endothelial cell regeneration

Authors	Cells/stem cells	Animal model	Duration	Efficacy
Garcia et al[37]	Autologous ADSC	Zucker DM rats	3 wk	Positive*
Huang et al[38]	Autologous ADSC	Dyslipidemic rats	4 wk	Partial
Qiu et al[39]	Rat BMSC	DM rats (STZ)	4 wk	Partial
Ryu et al[40]	Mouse AD-SVF	DM rats (STZ)	2 wk	Partial

ADSC: adipose tissue-derived stem cells, DM: diabetes mellitus, BMSC: bone marrow-derived stem cells, STZ: streptozotocin, AD-SVF: adipose tissue-derived stromal vascular fraction.
*Positive means that there was an increase in intracavernous pressure, but the authors compared erectile function with untreated diabetic animals and did not compare it with normal controls.

AD-SVF on diabetes-induced ED was not complete. Therefore, it is necessary to document whether modification of AD-SVF therapy, such as preconditioning of AD-SVF or combination with angiogenic factors, will result in complete restoration of erectile function.

CONCLUSIONS

Although many studies have so far demonstrated promising results with the use of protein, gene, or stem cells to enhance regeneration of the cavernous endothelial cells in a variety of animal models for vasculogenic ED, we are not yet at the point of beginning human trials. Along with identification of the novel molecule that promotes angiogenesis and combinations of potent angiogenic factors with or without stem cells, therapeutic angiogenesis will open new avenues for curing vasculogenic ED.

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