SEXUAL MEDICINE REVIEWS REVIEW

Suppression of Cavernosal Fibrosis in a Rat Model

Min Chul Cho, MD, PhD,[1] Won Hoon Song, MD,[2] and Jae-Seung Paick, MD, PhD[2]

ABSTRACT

Introduction: Cavernosal fibrosis is an important pathologic condition leading to erectile dysfunction (ED). The etiologies of cavernosal fibrosis include aging, diabetes mellitus, castration, cavernosal nerve injury during radical prostatectomy, hypertension, and Peyronie disease.

Aims: To summarize published studies investigating suppression of cavernosal fibrosis in rat models of ED of various etiologies.

Methods: A literature search was conducted using PubMed. Relevant studies were identified using search terms such as *erectile dysfunction*, *penis*, *fibrosis*, and *rat models*.

Main Outcome Measures: We reviewed representative literature studies on the mechanisms and suppression of cavernosal fibrosis in rat models of ED.

Results: The underlying mechanisms and potential therapeutic strategies suggested thus far for cavernosal fibrosis in rat models of ED were as follows. For age-related ED involving oxidative stress and tumor growth factor-β1 (TGF-β1)—driven pathways such as RhoA-ROCK1-LIMK2-cofilin or p42-44 and mitogen-activated protein kinase, proposed therapeutic strategies included phosphodiesterase type 5 inhibitors (PDE5Is), kallikrein-kinin system stimulators, and calorie restriction. For diabetes-related ED involving angiotensin-II— and TGF-β1—driven Smad and non-Smad pathways, TGF-β1-Wnt10b, and histone deacetylase (HDAC)-TGF-β1 pathways, positive therapeutic results were obtained with PDE5Is, TGF-β1 antagonists, HDAC inhibitors, antioxidants, sphingosine-1-phosphate receptor modulators (fingolimod), angiotensin-II antagonists, stem cell therapy, and antidiabetic drugs. For cavernosal nerve injury-associated ED involving TGF-β1—driven pathways (Smad or RhoA-ROCK1-LIMK2-cofilin), Sonic hedgehog signaling, angiotensin-II—Smad, and HDAC4—TGF-β1—Smad signaling triggered by cavernosal hypoxia, PDE5Is, angiotensin-II antagonists, stem cell therapy, HDAC inhibitors, Sonic hedgehog administration, ROCK inhibitors, and LIMK2 inhibitors have shown positive results. For testosterone deficiency-associated ED, TGF-β1—driven pathways were found to be responsive to testosterone supplementation. For hypertensive ED, positive therapeutic results were obtained with angiotensin-II antagonists. For Peyronie disease involving TGF-β1 or myostatin signaling, proposed therapeutic strategies included intra-tunical injection of TGF-β receptor inhibitors or adipose tissue-derived stem cells and HDAC2 small hairpin RNA.

Conclusion: Several signaling pathways appear to be responsible for the development of cavernosal fibrosis related to ED of various etiologies. Some therapeutic success has been achieved in animal models, but further research focusing on mechanism-specific targeted therapies is needed. **Cho MC, Song WH, Paick J-S. Suppression of Cavernosal Fibrosis in a Rat Model. Sex Med Rev 2018;X:XX—XX.**

Key Words: Erectile Dysfunction; Penis; Fibrosis; Rat

INTRODUCTION

Fibrosis is a pathologic feature of disease in virtually all organs.[1] Although a fibrogenic response might be adaptive in the short term,[1] excessive and/or prolonged responses lead to tissue scarring, cellular dysfunction, and organ failure.[1] Differentiation of fibroblasts into myofibroblasts, which produce extracellular matrix (ECM) proteins, is a hallmark of fibrosis.[2] Fibroblast-to-myofibroblast differentiation is induced by fibrogenic factors such as transforming growth factor-β (TGF-β), cytokines, and

Received December 30, 2017. Accepted February 27, 2018.

[1]Department of Urology, Seoul National University Boramae Medical Center, Seoul, Korea;

[2]Department of Urology, Seoul National University College of Medicine, Seoul, Korea

https://doi.org/10.1016/j.sxmr.2018.02.007

vasoactive peptides,[1–3] which are produced and/or activated by stimuli such as inflammation, injury, hyperglycemia, hypoxia, and apoptosis in the local environment.[1,2,4,5] Furthermore, apoptosis has been suggested to be required for TGF-β–induced fibrosis.[4,5] The copious production of ECM proteins by differentiated myofibroblasts ultimately leads to tissue fibrosis,[1,2] which can induce failure of most organs, including the penis and the heart.[1,6]

The etiologies of fibrosis of the penile corpus cavernosum (cavernosal fibrosis) include aging, diabetes mellitus (DM), hypertension, castration, radical prostatectomy (RP), Peyronie disease (PD), heavy smoking, alcoholism, explantation of a penile prosthesis, penile trauma, refractory low-flow priapism, and long-term intracavernous injection of vasoactive agents.[6–11] Cavernosal fibrosis is an important contributor to erectile dysfunction (ED).[12,13] Structural alterations of the cavernosum, such as fibrosis and apoptosis, contribute to the failure of the cavernosal tissue to expand and compress the subtunical venules and emissary veins against the tunica.[14,15] This results in venous leak and subsequent cavernosal veno-occlusive dysfunction (CVOD).[14,15] Penile fibrosis appears to occur by similar signaling mechanisms across all ED models of various etiologies.[6] The initial insult to the penile tissues results in the release of pro-fibrotic factors, mainly TGF-β1, other growth factors, vasoactive peptides, and reactive oxygen species, leading to oxidative stress, which in some cases be can exacerbated by chronic inflammation.[1,6] The pro-fibrotic factors lead to copious production of ECM proteins in the penile tissues through regulation of downstream signaling effectors, such as Smad, RhoA-ROCK, and mitogen-activated protein kinase (MAPK).[1,6]

Because cavernosal fibrosis is a causative factor of ED, several studies have been performed in animal models to investigate therapeutic strategies for the prevention and treatment of cavernosal fibrosis. In this review, we highlight the literature examining the underlying mechanisms and potential therapeutic options for suppression of cavernosal fibrosis in rat models of ED of various etiologies.

ANATOMY AND HISTOLOGY OF THE CORPUS CAVERNOSUM

The human corpora cavernosa are paired cylindrical structures within the penis. They are closely apposed for 3/4 of their length and are separated only by an incomplete connective tissue septum.[16,17] The cavernosa are enveloped by the tunica albuginea, which is a bilayer structure with multiple sublayers.[16] The crura corporis cavernosi are the proximal ends of the corpora cavernosa that originate at the undersurface of the ischiopubic rami.[16,17] Distally, they join under the pubic bone, are attached to the pubic arch, and their rounded ends meet the glans. The internal structure of the corpora cavernosa includes sinusoids, smooth muscle (SM) trabeculae, elastic fibers, collagen, intracavernous pillars, cavernosal and helicine arteries, and terminal branches of the cavernosal nerve (CN).[18] As the major structures of each corpus cavernosum, the sinusoids are separated by SM trabeculae and surrounded by collagen, elastin, fibroblasts, and loose areolar tissue.[18,19] The sinusoids dilate, allowing arterial blood to enter the central and peripheral sinusoids and fill the penis.[16] This expansion of the sinusoidal spaces causes the compression of subtunical venules against the tunica albuginea (cavernosal veno-occlusive mechanism), resulting in penile erection.[15,16] Histologically, the corpora cavernosa consist of trabecular SM (45%) and connective tissue (up to 50%).[20]

In rats, the corpora cavernosa are composed of multiple sinusoids of various sizes and interstitial tissues enveloped by the tunica albuginea. The endothelium-lined sinusoids are surrounded by SM. Figure 1 shows the morphologic changes in the corpus cavernosum during the progression of fibrosis.

CONDITIONS ASSOCIATED WITH CAVERNOSAL FIBROSIS

Cavernosal fibrosis is associated with various conditions, including aging, DM, CN injury during RP, castration, hypertension, and PD.[6–11] Although the precise mechanism of cavernosal fibrosis differs with each condition, there are some common characteristics, namely excessive accumulation or disorganization of collagen and other ECM proteins owing to increased differentiation of fibroblasts to myofibroblasts. The main factor eliciting this change is a tissue insult that can be acute and diffuse throughout the corpus cavernosum, as is observed with CN injury during RP, or chronic and diffuse throughout the corpus cavernosum and penile artery walls, as is the case for fibrosis associated with aging and DM.[6] Here, we discuss the molecular mechanisms and the proposed therapeutic strategies for suppression of cavernosal fibrosis induced by these conditions.

Aging

Age-related ED is caused by structural alterations, such as loss of cavernosal SMs, and progressive deposition of connective tissue, including collagen fibers.[21,22] These alterations reportedly result from increased oxidative stress induced by increased levels of reactive oxygen species, among other radicals.[23] A study by Ferrini et al[23] suggested that spontaneous induction of inducible nitric oxide synthase (iNOS) might protect against cavernosal fibrosis in aging rats. They administered L-N6-(1-iminoethyl)-lysine hydrochloride, a specific inhibitor of iNOS activity, to aged rats for 3 weeks and observed exacerbation of collagen fiber deposition within the penis, suggesting that decreased NO production intensifies age-related fibrosis.[23] Castela et al[24] showed that phosphorylation (activation) of p42-44 MAPK mostly occurred in SM cells in young rats but shifted to trabecular fibroblasts in the erectile tissue of elderly rats, indicating a potential role in ECM production. A role for TGF-β1, a potent fibrogenic molecule, in age-related cavernosal fibrosis was