Peyronie’s disease (PD) is characterized by plaque formation in the tunica albuginea (TA). Novel treatments are currently being developed to improve the treatment outcomes. In recent years, researchers in the field of male sexual dysfunction have studied stem cell therapy. Stem cells are undifferentiated cell populations that are capable of self-renewal and of differentiation into various kinds of cells or new tissues. In addition, stem cells also have antipoptotic, antifibrotic, and immunomodulatory properties. The results from preclinical studies support the potential role of adipose-derived stem cells (ADSCs) therapy for both the prevention and treatment of PD. However, there are several limitations of the animal model used in the studies. Further animal and clinical studies are still needed to validate the therapeutic effects and clinical application of ADSCs for the treatment of PD.

While the previous study focused on the early phase of PD to prevent TA fibrosis, Gokce et al. documented the beneficial effects of ADSCs injection in both the prevention and treatment groups (7). Autologous ADSCs were injected on the same day (prevention group) and 30 days (treatment group) following TGF-β1 injection. A local injection of ADSCs resulted in significant improvement of erectile function in both groups and were able to prevent or reduce Peyronie’s-like changes by decreasing the expression of tissue inhibitors of metalloproteinases (TIMPs), and by stimulating expression and activity of matrix metalloproteinases (MMPs). Because most PD patients presented in the chronic phase, the results of this study indicated that local injection of ADSCs might benefit most PD patients. Furthermore, this study used autologous ADSCs, which eliminated the concern regarding immune responses of the recipients.
Intralesional interferon α-2b is an alternative treatment option for PD patients. This drug class has the ability to regulate fibroblast function, reduce the production of extracellular collagen, and stimulate collagenase activity (8,9). The significant improvement in penile curvature, plaque size, and pain resolution were documented in the placebo-controlled study (10). Intratunical injections of genetically modified ADSCs with human interferon α-2b (ADSCs-IFN) were also evaluated in the rat model of TA fibrosis. In this study, there was a significant improvement in erectile response in the ADSCs-IFN group compared to ADSCs alone and also the placebo group (11). It appears that all available animal studies support the potential role of local ADSCs administration for the treatment of PD (Table 1). Further animal and clinical studies are needed to support these findings.

For surgical treatment of PD, allografts and xenografts (e.g., processed pericardium from a bovine or human source, porcine intestinal submucosa, and porcine skin) have been widely used for partial incision/excision and grafting. In this regard, ADSCs seeded small intestinal submucosa (ADSCs-SIS) was evaluated for TA reconstruction in a rat model of bilateral TA incision (12). Rats in the autologous ADSCs-SIS group maintained better erectile function compared to rats grafted with SIS alone. There was a significant increase in the expression of endothelial nitric oxide synthase (NOS) and neuronal NOS, and a reduced expression of inducible NOS in the cavernosal tissue of the ADSCs-SIS group. These findings suggest that ADSCs improve the recovery of TA and erectile function by enhancing angiogenesis and decreasing fibrosis.

Conclusions

The results from preclinical studies support the potential role of ADSCs therapy for both prevention and treatment of PD. Because of the limitations of the animal model used, most studies have focused on the treatment of PD-associated erectile dysfunction. Currently, no studies report the significant improvement of plaque size or penile curvature, which is considered the main objective of PD treatment. Further animal and clinical studies are needed to validate the therapeutic benefits of ADSCs for the treatment of PD.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Bunnell BA, Flaat M, Gagliardi C, et al. Adipose-derived stem cells: isolation, expansion and differentiation. Methods 2008;45:115-20.
2. Alfaro-C, Roubeix C, Chaaya R, et al. Intraperitoneal injection of bone marrow mesenchymal stem cells reduces kidney fibrosis after ischemia-reperfusion in cyclosporine-immunosuppressed rats. Cell Transplant 2012;21:2009-19.
3. Zhao W, Li JJ, Cao DY, et al. Intravenous injection of mesenchymal stem cells is effective in treating liver fibrosis. World J Gastroenterol 2012;18:1048-58.
4. Moodley Y, Atienza D, Manuelpillai U, et al. Human umbilical cord mesenchymal stem cells reduce fibrosis of bleomycin-induced lung injury. Am J Pathol

Table 1 Summary of stem cell-based studies in Peyronie's-like conditions

| Study                | Year | Animal model                  | Type of stem cells | Results                                                                 |
|----------------------|------|--------------------------------|--------------------|-------------------------------------------------------------------------|
| Castiglione et al.   | 2013 | TA fibrosis (Prevention)       | Human ADSCs        | - Improve erectile function                                              |
|                      |      |                                |                    | - Prevent upregulation of collagen type III and elastin                 |
| Gokce et al. (7)     | 2014 | TA fibrosis (Prevention and treatment) | Rat ADSCs | - Improve erectile function                                               |
|                      |      |                                |                    | - Prevent and/or reduce Peyronie's-like changes                          |
| Gokce et al. (11)    | 2015 | TA fibrosis (Prevention and treatment) | Rat ADSCs with interferon α-2b | - Improve erectile function                                               |
|                      |      |                                |                    | - Reduce Peyronie's-like changes                                         |
| Ma et al. (12)       | 2012 | TA incisions                   | Rat ADSCs seeded SIS | - Improve erectile function                                               |
|                      |      |                                |                    | - Increase expression of endothelial NOS and neuronal NOS               |

ADSCs, adipose-derived stem cells.
5. Castiglione F, Hedlund P, Van der Aa F, et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie’s disease. Eur Urol 2013;63:551-60.

6. Castiglione F, Hedlund P, Van der Aa F, et al. Reply from Authors re: Ching-Shwun Lin, Tom F. Lue. Adipose-derived Stem Cells for the Treatment of Peyronie’s Disease? Eur Urol 2013;63:561-2: Xenogeneic Adipose Stem Cell Treatment in a Rat Model of Peyronie’s Disease. Eur Urol 2013;63:563-4.

7. Gokce A, Abd Elmageed ZY, Lasker GF, et al. Adipose tissue-derived stem cell therapy for prevention and treatment of erectile dysfunction in a rat model of Peyronie’s disease. Andrology 2014;2:244-51.

8. Levine LA, Burnett AL. Standard operating procedures for Peyronie’s disease. J Sex Med 2013;10:230-44.

9. Ahuja S, Bivalacqua TJ, Case J, et al. A pilot study demonstrating clinical benefit from intralesional interferon alpha 2B in the treatment of Peyronie’s disease. J Androl 1999;20:444-8.

10. Hellstrom WJ, Kendirci M, Matern R, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie’s disease. J Urol 2006;176:394-8.

11. Gokce A, Abd Elmageed ZY, Lasker GF, et al. Intratunical Injection of Genetically Modified Adipose Tissue-Derived Stem Cells with Human Interferon α-2b for Treatment of Erectile Dysfunction in a Rat Model of Tunica Albugineal Fibrosis. J Sex Med 2015;12:1533-44.

12. Ma L, Yang Y, Sikka SC, et al. Adipose tissue-derived stem cell-seeded small intestinal submucosa for tunica albuginea grafting and reconstruction. Proc Natl Acad Sci U S A 2012;109:2090-5.

Cite this article as: Sangkum P. Research highlights on stem cell therapy for the treatment of Peyronie’s disease. Transl Androl Urol 2016;5(3):363-365. doi: 10.21037/tau.2016.03.14